



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p>(21) International Application Number: PCT/US91/08648</p> <p>(22) International Filing Date: 25 November 1991 (25.11.91)</p> <p>(30) Priority data: 626,590 11 December 1990 (11.12.90) US</p> <p>(60) Parent Application or Grant (63) Related by Continuation US 626,590 (CON) Filed on 11 December 1990 (11.12.90)</p> <p>(71) Applicant (for all designated States except US): G.D. SEARLE &amp; CO. [US/US]; Corporate Patent Department, P.O. Box 5110, Chicago, IL 60680-5110 (US).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): BECKER, Daniel, Paul [US/US]; 1427 Pebble Creek Drive, Glenview, IL 60025 (US). FLYNN, Daniel, Lee [US/US]; 17 North Bristol Court, Mundelein, IL 60060 (US). VILLAMIL, Clara, Ines [CO/US]; 813 Long Road, Glenview, IL 60025 (US).</p>		<p>(74) Agents: SERAUSKAS, Joy, A. et al.; G.D. Searle &amp; Co., Corporate Patent Department, P.O. Box 5110, Chicago, IL 60680-5110 (US).</p> <p>(81) Designated States: AT, AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH, CH (European patent), CI (OAPI patent), CM (OAPI patent), CS, DE, DE (European patent), DK, DK (European patent), ES, ES (European patent), FI, FR (European patent), GA (OAPI patent), GB, GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU, LU (European patent), MC, MG, ML (OAPI patent), MN, MR (OAPI patent), MW, NL, NL (European patent), NO, PL, RO, SD, SE, SE (European patent), SN (OAPI patent), SU*, TD (OAPI patent), TG (OAPI patent), US.</p> <p><b>Published</b> With international search report.</p>
<p>(54) Title: N-SUBSTITUTED LACTAMS USEFUL AS CHOLECYSTOKININ ANTAGONISTS</p> <div style="text-align: center; margin: 20px 0;"> <p style="text-align: right;">(I)</p> </div> <p>(57) Abstract</p> <p>This invention relates to novel N-substituted lactams having formula (I) useful in the treatment and prevention of cholecystokinin (CCK) related disorders of the gastrointestinal, central nervous and appetite regulatory systems of mammals.</p>		

# + DESIGNATIONS OF "SU"

Any designation of "SU" has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.

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N-SUBSTITUTED LACTAMS  
USEFUL AS CHOLECYSTOKININ  
ANTAGONISTS

FIELD OF THE INVENTION

The invention herein is directed to N-substituted lactams which can be useful in the treatment and prevention of cholecystokinin (CCK) related disorders of the gastrointestinal, central nervous and appetite regulatory systems of mammals by administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein or a pharmaceutically acceptable salt thereof. Therefore, the compounds of the invention find utility in GI motility disorders including irritable bowel syndrome, visceral pain, reversing satiety, and in treating anxiety. Also, the compounds of the invention are useful in the treatment of pancreatitis and pancreatic cancer.

Background of the Invention

Cholecystokinin (CCK) is a brain/gut neuropeptide which has been implicated in a number of central nervous system and gastrointestinal disease states [Reviews: J. A. Williams, Biomedical Research (1982), 3, 107; M. Albus, Prog. Neuro-Psychopharmacol & Biol. Psychiat. (1988), 12, p S5].

Cholecystokinin in the GI tract evokes contraction of gut smooth musculature [U. Scheurer et al, Am. J. Physiol. (1983,

244, G266], and functionally causes delayed gastric emptying, contraction of the gall bladder [E. Corazziari et al, Dig. Dis. & Sci. (1990), 35, 50], initiation of the gastrocolic reflex [R. F. Harvey and A. E. Read, The Lancet (1973), Sat. 6 January, p. 7793]. CCK plays an important physiologic role in pancreatic function and secretion. Abnormalities of CCK have been implicated in causing pancreatitis [C. Niederau et al, Gastroenterology (1985), 88, 1192]. Abnormalities of CCK function in the GI tract may be causative in a number of GI motility disorders, including irritable bowel syndrome. Additionally, CCK acts as a physiologic opiate antagonist, and has been reported to be hyperalgesic, and to inhibit analgesia produced by opiates [P. L. Faris et al, Science (1983), 219, 310; N. S. Baber et al, Pain (1989), 39, 307].

Actions of CCK in the central nervous system have demonstrated a role for CCK in controlling eating behavior (producing satiety) [G. P. Smith in Eating and Its Disorders (A. J. Stunkard & E. Stellar, Eds), (1984), pp. 67-75, Raven Press], in producing symptoms of panic disorder & other forms of anxiety [Trends in Pharmacol. Sci. (1990), 11, 271], and in modulating mesolimbic dopamine release [J. N. Crawley in



Cholecystokinin Antagonists (R. Y. Wang R. Schoenfeld, eds., (1988), pp. 243-262, Alan R. Liss].

Finally, CCK and/or gastrin have been implicated as tumorigenic in a number of cancers, including cancers of the pancreas and the colon [S. A. Watson et al, GUT (1989, 30, 1447; B. R. Douglas et al, Cancer Research (1989), 49, 2438].

Thus, an antagonist to CCK at either the A-receptor subtype or the B-receptor subtype may be useful in the treatment of GI motility disorders (including irritable bowel syndrome), eating disorders where an anti-satiety effect is desired, panic-like anxiety, compulsive behavior and other CNS disorders.

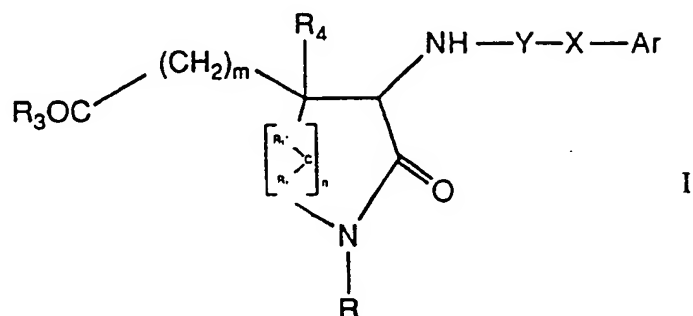
United States Patent 4,757,068 discloses a class of lactams and bicyclic lactams which are useful in the treatment and prevention of CCK-related disorders of the gastrointestinal, central nervous and appetite regulatory systems of mammals. The compounds of this disclosure are structurally distinct from the present invention.

bicyclic  $\beta$ -lactam penicillin analogs having anti-bacterial activity. The compounds of this disclosure are distinct from the compounds of the present invention both in structure and utility.

United States Patent 3,474,093 discloses pyrrolidinone, indolinone, cycloheptapyrrolone and cyclopentapyrrolone adducts of N-acyloxy-N-acylaminoacetanilides useful as hyperemic depressants, anti-convulsants and antiarrhythmic agents.

SUMMARY OF THE INVENTION

The present invention relates to a novel class of compounds represented by the formula



and isomers thereof; or a pharmaceutically acceptable acid or base addition salt thereof:

wherein

Ar is

aryl;

substituted aryl which can be substituted one or more by alkyl of 1 to 6 carbon atoms, alkoxy

wherein the alkyl is 1 to 6 carbon atoms,

trifluoromethyl, halogen, amino, alkyl or dialkyl

substituted amino wherein the alkyl is 1 to 6

carbon atoms; heterounsaturated ring having 5 or 6 carbon atoms wherein one or two of the carbon atoms is replaced by nitrogen, oxygen or sulfur; substituted heterounsaturated ring having 5 or 6 carbon atoms wherein one or two of the carbon atoms is replaced by nitrogen, oxygen or sulfur which can be substituted once or more by alkyl of 1 to 6 carbon atoms, halogen or trifluoromethyl; fused bicyclic aromatic hydrocarbon radical having 9 or 10 carbon atoms; substituted fused bicyclic aromatic hydrocarbon radical having 9 or 10 carbon atoms which can be substituted one or more by alkyl of 1 to 6 carbon atoms, halogen, trifluoromethyl, amino, alkyl or dialkyl substituted amino wherein the alkyl is 1 to 6 carbon atoms or alkoxy wherein the alkyl is 1 to 6 carbon atoms; fused heterobicyclic hydrocarbon radical having 9 or 10 carbon atoms wherein one to three of the carbon atoms is replaced by nitrogen, oxygen or sulfur; substituted fused heterobicyclic hydrocarbon radical having 9 or 10 carbon atoms wherein one to three of the carbon atoms is replaced by nitrogen oxygen or sulfur which can be substituted one or

more by alkyl of 1 to 6 carbon atoms, halogen, trifluoromethyl, amino, alkyl or dialkyl substituted amino wherein the alkyl is 1 to 6 carbon atoms or alkoxy wherein the alkyl is 1 to 6 carbon atoms.

R is  
alkyl having 1 to 8 carbon atoms wherein one of the carbon atoms may be replaced by oxygen;  
aryl;  
substituted aryl which can be substituted one or more by halogen, alkyl having 1 to 6 carbon atoms, alkoxy wherein the alkyl is 1 to 6 carbon atoms, amino, alkyl or dialkyl substituted amino wherein the alkyl is 1 to 6 carbon atoms, trifluoromethyl, or methylene dioxy; aralkyl wherein the alkyl is 1 to 8 carbon atoms; substituted aralkyl wherein the alkyl is 1 to 8 carbon atoms and the substituent or substituents are selected from the group consisting of halogen, alkyl having 1 to 6 carbon atoms, alkoxy wherein the alkyl is 1 to 6 carbon atoms, amino, alkyl or dialkyl substituted amino wherein

the alkyl is 1 to 6 carbon atoms, trifluoromethyl, or methylene dioxy.

X is a direct bond or a substituent selected from the group consisting of NH, oxygen or alkylene having 1 to 3 carbon atoms.

n is an integer from 0 to 1.

R<sub>1</sub> and R'<sub>1</sub> are each independently hydrogen or alkyl having 1 to 4 carbon atoms.

m is an integer from 0 to 3

R<sub>3</sub> is OH, OR<sub>5</sub> wherein R<sub>5</sub> is alkyl having 1 to 6 carbon atoms, NR<sub>6</sub>R<sub>7</sub> wherein R<sub>6</sub> and R<sub>7</sub> are each independently hydrogen or alkyl of 1 to 6 carbon atoms or NR<sub>8</sub>R<sub>9</sub> which together form a five to seven membered ring wherein R<sub>8</sub> and R<sub>9</sub> represent an alkylene group having four to six carbon atoms and one of the alkylenes may be optionally replaced by oxygen, nitrogen or NR<sub>10</sub> wherein R<sub>10</sub> represents hydrogen, or alkyl having 1 to 6 carbon atoms or aralkyl wherein the alkyl is 1 to 6 carbon atoms.

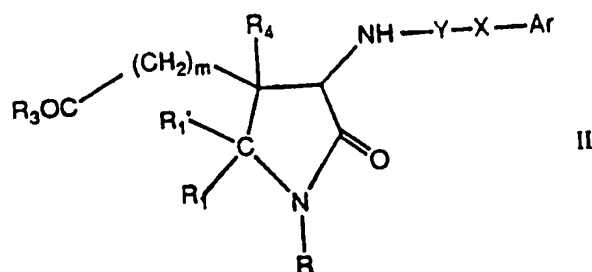
R<sub>4</sub> is hydrogen or alkyl having 1 to 4 carbon atoms.

Y is C=O or SO<sub>2</sub>.

The invention further relates to pharmaceutical compositions comprising a compound of formula I. Such

compounds and compositions can be useful in the treatment and prevention of cholecystokinin (CCK) related disorders of the gastrointestinal, central nervous and appetite regulatory systems.

A preferred embodiment of the present invention are compounds of the formula



and isomers thereof; or a pharmaceutically acceptable acid or base addition salt thereof:

wherein

Ar is

aryl;

substituted aryl which can be substituted one or more by alkyl of 1 to 6 carbon atoms, alkoxy

wherein the alkyl is 1 to 6 carbon atoms, trifluoromethyl, halogen, amino, alkyl or dialkyl substituted amino wherein the alkyl is 1 to 6 carbon atoms; heterounsaturated ring having 5 or 6 carbon atoms wherein one or two of the carbon atoms is replaced by nitrogen, oxygen or sulfur; substituted heterounsaturated ring having 5 or 6 carbon atoms wherein one or two of the carbon atoms is replaced by nitrogen, oxygen or sulfur which can be substituted once or more by alkyl of 1 to 6 carbon atoms, halogen or trifluoromethyl; fused bicyclic aromatic hydrocarbon radical having 9 or 10 carbon atoms; substituted fused bicyclic aromatic hydrocarbon radical having 9 or 10 carbon atoms which can be substituted one or more by alkyl of 1 to 6 carbon atoms, halogen, trifluoromethyl, amino, alkyl or dialkyl substituted amino wherein the alkyl is 1 to 6 carbon atoms or alkoxy wherein the alkyl is 1 to 6 carbon atoms; fused heterobicyclic hydrocarbon radical having 9 or 10 carbon atoms wherein one to three of the carbon atoms is replaced by nitrogen, oxygen or sulfur; substituted fused heterobicyclic hydrocarbon



radical having 9 or 10 carbon atoms wherein one to three of the carbon atoms is replaced by nitrogen oxygen or sulfur which can be substituted one or more by alkyl of 1 to 6 carbon atoms, halogen, trifluoromethyl, amino, alkyl or dialkyl substituted amino wherein the alkyl is 1 to 6 carbon atoms or alkoxy wherein the alkyl is 1 to 6 carbon atoms.

R is  
alkyl having 1 to 8 carbon atoms wherein one of the carbon atoms may be replaced by oxygen;  
aryl;  
substituted aryl which can be substituted one or more by halogen, alkyl having 1 to 6 carbon atoms, alkoxy wherein the alkyl is 1 to 6 carbon atoms, amino, alkyl or dialkyl substituted amino wherein the alkyl is 1 to 6 carbon atoms, trifluoromethyl, or methylene dioxy; aralkyl wherein the alkyl is 1 to 8 carbon atoms; substituted aralkyl wherein the alkyl is 1 to 8 carbon atoms and the substituent or substituents are selected from the group consisting of halogen, alkyl having 1 to 6 carbon atoms,

alkoxy wherein the alkyl is 1 to 6 carbon atoms, amino, alkyl or dialkyl substituted amino wherein the alkyl is 1 to 6 carbon atoms, trifluoromethyl or methylene dioxy.

X is a direct bond or a substituent selected from the group consisting of NH, oxygen or alkylene having 1 to 3 carbon atoms.

$R_1$  and  $R_1'$  are each independently hydrogen or alkyl having 1 to 4 carbon atoms.

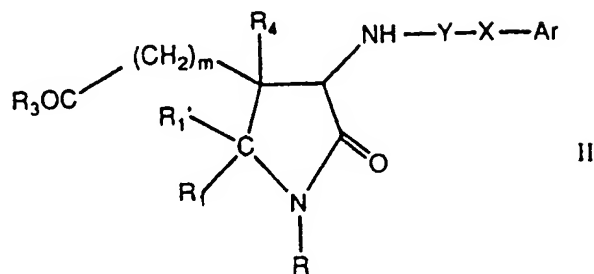
m is an integer from 0 to 3

$R_3$  is OH,  $OR_5$  wherein  $R_5$  is alkyl having 1 to 6 carbon atoms,  $NR_6R_7$  wherein  $R_6$  and  $R_7$  are each independently hydrogen or alkyl of 1 to 6 carbon atoms or  $NR_8R_9$  which together form a five to seven membered ring wherein  $R_8$  and  $R_9$  represent an alkylene group having four to six carbon atoms and one of the alkylenes may be optionally replaced by oxygen, nitrogen or  $NR_{10}$  wherein  $R_{10}$  represents hydrogen, or alkyl having 1 to 6 carbon atoms or aralkyl wherein the alkyl is 1 to 6 carbon atoms.

$R_4$  is hydrogen or alkyl having 1 to 4 carbon atoms.

Y is C=O or  $SO_2$ .

A further preferred embodiment of the present invention are compounds of the formula



and isomers thereof; or a pharmaceutically acceptable acid or base addition salt thereof:

wherein

Ar is

aryl;

substituted aryl which can be substituted one or more by alkyl of 1 to 6 carbon atoms, alkoxy

wherein the alkyl is 1 to 6 carbon atoms,

trifluoromethyl, halogen, amino, or alkyl or

dialkyl substituted amino wherein the alkyl is 1 to

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6 carbon atoms; heterounsaturated ring having 5 or 6 carbon atoms wherein one or two of the carbon atoms is replaced by nitrogen, oxygen or sulfur; substituted heterounsaturated ring having 5 or 6 carbon atoms wherein one or two of the carbon atoms is replaced by nitrogen, oxygen or sulfur which can be substituted once or more by alkyl of 1 to 6 carbon atoms, halogen or trifluoromethyl;

R is

alkyl having 1 to 8 carbon atoms;

aryl;

substituted aryl which can be substituted one or more by halogen, alkyl having 1 to 6 carbon atoms, alkoxy wherein the alkyl is 1 to 6 carbon atoms, amino, alkyl or dialkyl substituted amino wherein the alkyl is 1 to 6 carbon atoms, trifluoromethyl or methylene dioxy or; aralkyl wherein the alkyl is 1 to 8 carbon atoms.

$R_1$  and  $R_1'$  are each independently hydrogen or alkyl having 1 to 4 carbon atoms.

m is an integer from 0 to 3

$R_3$  is OH or  $OR_5$  wherein  $R_5$  is alkyl having 1 to 6 carbon atoms.

R<sub>4</sub> is hydrogen

X is a direct bond or a substituent selected from the group consisting of NH, oxygen or alkylene having 1 to 3 carbon atoms.

Y is C=O or SO<sub>2</sub>.

Exemplifying this embodiment are the following compounds.

cis-4-[[ (3,4-dichlorophenyl) carbonyl] amino]-5-oxo-1-pentyl-3-pyrrolidinecarboxylic acid.

trans-4-[[ (4-chlorophenyl) carbonyl] amino]-5-oxo-1-pentyl-3-pyrrolidinecarboxylic acid.

trans-4-[[ [(4-chlorophenyl) amino] carbonyl] amino]-5-oxo-1-pentyl-3-pyrrolidinecarboxylic acid.

cis-4-[[ [(4-chlorophenyl) amino] carbonyl] amino]-5-oxo-1-pentyl-3-pyrrolidinecarboxylic acid.

cis-4-[[ [(3,4-dichlorophenyl) amino] carbonyl] amino]-5-oxo-1-pentyl-3-pyrrolidinecarboxylic acid.

cis-4-[[ (4-chlorophenyl) carbonyl] amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid.

trans-4-[[ (4-chlorophenyl) carbonyl] amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid.

cis-4-[[ (3,4-dichlorophenyl) carbonyl] amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid.

trans-4-[[ (3,4-dichlorophenyl) carbonyl] amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid.

trans-4-[[ [(3,4-dichlorophenyl) amino] carbonyl] amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid.

cis-4-[[ [(3,4-dichlorophenyl) amino] carbonyl] amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid.

cis-4-[[ (3,4-dichlorophenyl) sulfonyl] amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid.

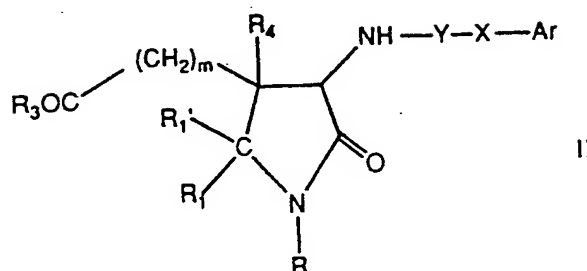
cis-5-oxo-1-phenyl-4-[(2-pyrazinyl carbonyl) amino]-3-pyrrolidinecarboxylic acid

cis-4-[[ (3,4-dichlorophenyl) carbonyl] amino]-5-oxo-1-(phenylmethyl)-3-pyrrolidinecarboxylic acid

cis-4-[[ [ (3,4-dichlorophenyl) amino] carbonyl] amino]-5-oxo-1-(methylphenyl)-3-pyrrolidinecarboxylic acid

trans-4-[[ [ (4-chlorophenyl) amino] carbonyl] amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid

Another preferred embodiment of the present invention are compounds of the formula



and isomers thereof; or a pharmaceutically acceptable acid or base addition salt thereof:

wherein

Ar is

fused bicyclic aromatic hydrocarbon radical having 9 or 10 carbon atoms; substituted fused bicyclic aromatic hydrocarbon radical having 9 or 10 carbon atoms which can be substituted one or more by alkyl of 1 to 6 carbon atoms, halogen, trifluoromethyl amino, alkyl or dialkyl substituted amino wherein



the alkyl is 1 to 6 carbon atoms, or alkoxy wherein the alkyl is 1 to 6 carbon atoms.

R is

alkyl having 1 to 8 carbon atoms;

aryl;

substituted aryl which can be substituted one or more by halogen, alkyl having 1 to 6 carbon atoms, alkoxy wherein the alkyl is 1 to 6 carbon atoms, amino, alkyl or dialkyl substituted amino wherein the alkyl is 1 to 6 carbon atoms, trifluoromethyl, or methylene dioxy; aralkyl wherein the alkyl is 1 to 8 carbon atoms; substituted aralkyl wherein the alkyl is 1 to 8 carbon atoms and the substituent or substituents are selected from the group consisting of halogen, alkyl having 1 to 6 carbon atoms, alkoxy wherein the alkyl is 1 to 6 carbon atoms, amino, alkyl or dialkyl substituted amino wherein the alkyl is 1 to 6 carbon atoms, trifluoromethyl, or methylene dioxy;

$R_1$  and  $R_1'$  are each independently hydrogen or alkyl having 1 to 4 carbon atoms.

m is an integer from 0 to 3

$R_3$  is OH,  $OR_5$  wherein  $R_5$  is alkyl having 1 to 6 carbon atoms,  $NR_6R_7$  wherein  $R_6$  and  $R_7$  are each independently hydrogen or alkyl of 1 to 6 carbon atoms or  $NR_8R_9$  which together form a five to seven membered ring wherein  $R_8$  and  $R_9$  represent an alkylene group having four to six carbon atoms and one of the alkylenes may be optionally replaced by oxygen, nitrogen or  $NR_{10}$  wherein  $R_{10}$  represents hydrogen, or alkyl having 1 to 6 carbon atoms or aralkyl wherein the alkyl is 1 to 6 carbon atoms.

$R_4$  is hydrogen

$Y$  is  $C=O$  or  $SO_2$

$X$  is a direct bond or a substituent selected from the group consisting of NH, oxygen or alkylene having 1 to 3 carbon atoms.

Exemplifying this embodiment are the following compounds:

trans-4-[(2-naphthalenylcarbonyl)amino-5-oxo-1-pentyl-3-pyrrolidinecarboxylic acid.

cis-1-[(2-fluorophenyl)-4-[(2-naphthalenylcarbonyl)amino]-5-oxo-3-pyrrolidinecarboxylic acid.

cis-4-[[ (2-naphthalenylamino) carbonyl] amino]-5-oxo-1-pentyl-3-pyrrolidinecarboxylic acid.

cis-4-[(2-naphthalenylcarbonyl) amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid.

trans-4-[(2-naphthalenylcarbonyl) amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid.

cis-1-[[3-[(2-naphthalenylcarbonyl) amino]-2-oxo-1-phenyl-4-pyrrolidinyl]carbonyl]pyrrolidine

trans-1-[[3-[(2-naphthalenylcarbonyl) amino]-2-oxo-1-phenyl-4-pyrrolidinyl]carbonyl]pyrrolidine

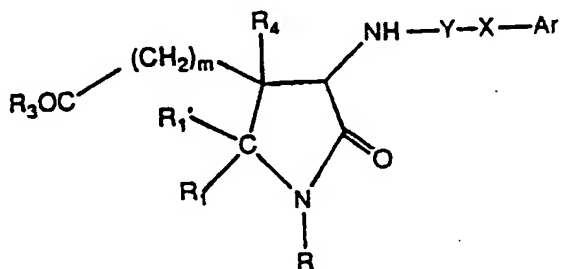
trans-4-[[ (2-naphthalenylamino) carbonyl] amino)-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid

1,1-dimethylethyl cis-4-[(2-naphthalenylcarbonyl)amino]-  
5-oxo-1-phenyl-3-pyrrolidinecarboxylate

cis-4-[(2-naphthalenylcarbonyl)amino]-5-oxo-1-  
(phenylmethyl)-3-pyrrolidinecarboxylic acid

cis-4-[(2-naphthalenylsulfonyl)amino]-5-oxo-1-phenyl-3-  
pyrrolidinecarboxylic acid

Another further preferred embodiment of the present  
invention are compounds of the formula



and isomers thereof; or a pharmaceutically acceptable acid or  
base addition salt thereof:

wherein

Ar is

fused heterobicyclic hydrocarbon radical having 9 or 10 carbon atoms wherein one to three of the carbon atoms is replaced by nitrogen, oxygen or sulfur; substituted fused heterobicyclic hydrocarbon radical having 9 or 10 carbon atoms wherein one to three of the carbon atoms is replaced by nitrogen oxygen or sulfur which can be substituted one or more by alkyl of 1 to 6 carbon atoms, halogen, trifluoromethyl, amino, alkyl or dialkyl substituted amino wherein the alkyl is 1 to 6 carbon atoms, or alkoxy wherein the alkyl is 1 to 6 carbon atoms.

R is  
alkyl having 1 to 8 carbon atoms;  
aryl;  
substituted aryl which can be substituted one or more by halogen, alkyl having 1 to 6 carbon atoms, alkoxy wherein the alkyl is 1 to 6 carbon atoms, amino, alkyl or dialkyl substituted amino wherein the alkyl is 1 to 6 carbon atoms, trifluoromethyl, or methylene dioxy; aralkyl wherein the alkyl is 1 to 8 carbon atoms; substituted aralkyl wherein the

alkyl is 1 to 8 carbon atoms and the substituent or substituents are selected from the group consisting of halogen, alkyl having 1 to 6 carbon atoms, alkoxy wherein the alkyl is 1 to 6 carbon atoms, amino, alkyl or dialkyl substituted amino wherein the alkyl is 1 to 6 carbon atoms, trifluoromethyl, or methylene dioxy.

$R_1$  and  $R_1'$  are each independently hydrogen or alkyl having 1 to 4 carbon atoms.

$m$  is an integer from 0 to 3

$R_3$  is OH,  $OR_5$  wherein  $R_5$  is alkyl having 1 to 6 carbon atoms,  $NR_6R_7$  wherein  $R_6$  and  $R_7$  are each independently hydrogen or alkyl of 1 to 6 carbon atoms or  $NR_8R_9$  which together form a five to seven membered ring wherein  $R_8$  and  $R_9$  represent an alkylene group having four to six carbon atoms and one of the alkylenes may be optionally replaced by oxygen, nitrogen or  $NR_{10}$  wherein  $R_{10}$  represents hydrogen, or alkyl having 1 to 6 carbon atoms or aralkyl wherein the alkyl is 1 to 6 carbon atoms.

$R_4$  is hydrogen

$Y$  is C=O

X is a direct bond or a substituent selected from the group consisting of NH, oxygen or alkylene having 1 to 3 carbon atoms.

Exemplifying this embodiment are the following compounds:

trans-N-[2-oxo-1-phenyl-4-(1-pyrrolidinylcarbonyl)-3-pyrrolidinyl]-1H-indole-2-carboxamide

cis-4-[(1H-indol-2-ylcarbonyl)amino]-5-oxo-1-(phenylmethyl)-3-pyrrolidinecarboxylic acid

cis-4-[(1H-indazol-3-ylcarbonyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid

cis-4-[(1H-indol-2-ylcarbonyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid.

cis-1-(2-fluorophenyl)-5-oxo-4-[(3-quinolinylcarbonyl)amino]-5-oxo-3-pyrrolidinecarboxylic acid.

trans-4-[(1-H-indol-3-acetyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid.

cis-5-oxo-1-pentyl-4-[(3-quinolinylcarbonyl)amino]-3-pyrrolidinecarboxylic acid, monohydrochloride.

trans-4-[(1H-indol-2-ylcarbonyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid.

As used herein, the term "alkyl of 1 to 8 carbon atoms" refers to straight chain or branched chain hydrocarbon groups having from 1 to 8 carbon atoms. Illustrative of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, neopentyl, hexyl, isohexyl and octyl.

As used herein, the term "alkoxy wherein the alkyl is 1 to 6 carbon atoms" refers to straight or branched chain ethers. Illustrative of such groups are methoxy, ethoxy, propoxy, butoxy and isopropoxy.

As used herein, the term "amino" refers to the group -NH<sub>2</sub>; "alkyl or dialkyl substituted amino wherein the alkyl is



1 to 6 carbon atoms" refers to the replacement of hydrogen by an alkyl group.

As used herein, the term "alkylene having 1 to 3 carbon atoms" refers to straight or branched saturated hydrocarbon groups having from one to three carbon atoms. Illustrative of such groups are methylene, ethylene, trimethylene, and methylethylene.

The term "aryl" represents phenyl or biphenyl.

As used herein, the term "halogen" includes fluoro, chloro and bromo.

As used herein, the term " $\text{NR}_8\text{R}_9$  which together form a five to seven membered ring wherein  $\text{R}_8$  and  $\text{R}_9$  represent an alkylene group having four to six carbon atoms and one of the alkylenes may be optionally replaced by oxygen, nitrogen or  $\text{NR}_{10}$  wherein  $\text{R}_{10}$  represents hydrogen, or alkyl having 1 to 6 carbon atoms or aralkyl wherein the alkyl is 1 to 6 carbon atoms" refers to heterosaturated cyclic radical having 5 to 7 atoms wherein one of the atoms is nitrogen and the remaining atoms are alkylenes wherein one of the alkylenes may be

optionally replaced by oxygen, nitrogen or  $\text{NR}_{10}$  wherein  $\text{R}_{10}$  is defined as above. Illustrative of such radicals are morpholinyl, pyrazolinyl, piperazinyl and 4-methyl piperizinyl.

As used herein, the term "heterounsaturated ring having 5 or 6 carbon atoms wherein one or two of the carbon atoms is replaced by nitrogen, sulfur or oxygen" refers to a heterounsaturated cyclic radical having 5 or 6 carbon atoms wherein one or two of the carbons is replaced by nitrogen, sulfur or oxygen. Illustrative of such radicals are pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyranyl, furanyl, thiophenyl, isothiazolyl, isoxazolyl, pyrazolinyl, and imidazolinyl, oxazolyl, and thiazolyl.

As used herein, the term "fused bicyclic aromatic hydrocarbon radical having 9 or 10 carbon atoms" refers to aromatic hydrocarbons composed of two fused rings having a maximum number of 10 carbons. Illustrative of such radicals are naphthalenyl and indenyl.

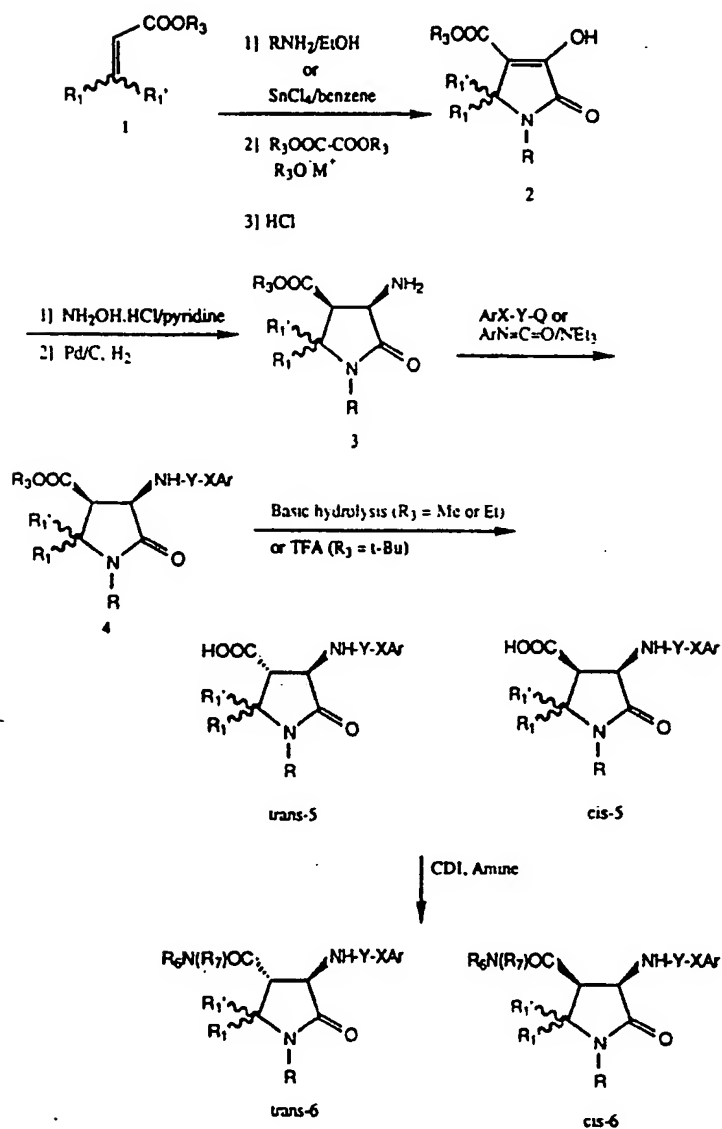
As used herein, the term "fused heterobicyclic hydrocarbon radical having 9 or 10 carbon atoms wherein one to three of the carbon atoms is replaced by nitrogen, oxygen or sulfur" refers to hydrocarbons composed of two fused rings having a maximum of 10 carbons wherein one to three of the carbon atoms is replaced by nitrogen, oxygen or sulfur. Illustrative of such radicals are indoliziny1, isoindolyl, indolyl, indazolyl, benzofuranyl, isobenzofuranyl, chromenyl, benzothiophenyl, quinoliziny1, isoquinoliny1, quinoliny1, imidazopyridiny1, pyridinopyridiny1, phthalaziny1, naphthyridiny1, indoliny1, and chromany1.

Included within the embodiments of the present invention are the tautomeric forms of the described compounds, isomeric forms including geometric isomers, enantiomers and diastereoisomers, and the pharmaceutically acceptable salts thereof.

The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. Since the compounds of Formulas I, II and III contain basic nitrogen atoms, such salts are typically acid addition salts or quaternary salts. The nature of the salt is not critical,

provided that it is pharmaceutically acceptable, and acids which may be employed to form such salts are, of course, well known to those skilled in this art. Examples of acids which may be employed to form pharmaceutically acceptably acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid, and such organic acids as maleic acid, succinic acid and citric acid. Other pharmaceutically acceptably salts include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium and magnesium, or with organic bases, such as dicyclohexylamine. All of these salts may be prepared by conventional means by reacting, for example, the appropriate acid or base with the corresponding compound of Formulas I, II and III.

## SCHEME I: SYNTHESIS OF PYRRIDINONE CCK ANTAGONISTS

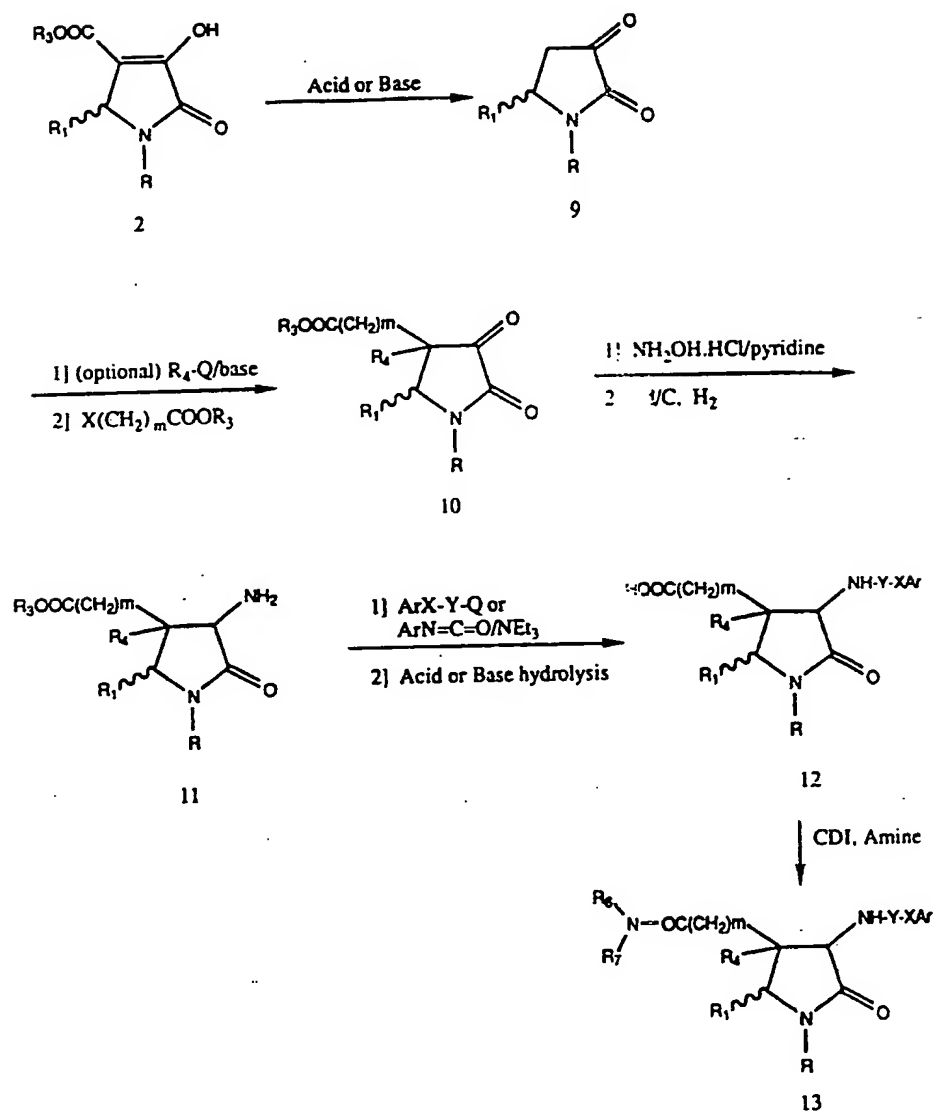


The synthesis of compounds of Formula I wherein n equals 1 and R, R<sub>1</sub>, R'<sub>1</sub>, Ar, m, Y and X are defined as before and R<sub>2</sub> is hydrogen, R<sub>3</sub> is C<sub>3</sub> or OR<sub>3</sub> wherein R<sub>3</sub> is alkyl of 1 to 6 carbon atoms and (Scheme I) involves the use of methodology reported by Southwick et al. [J. Org. Chem. 21, 1087 (1956) & J. Am. Chem. Soc. 75, 3413 (1953)] for the preparation of intermediate 2. Thus the appropriate acrylate ester 1 optionally mono- or di-substituted in the beta position is reacted with the desired aliphatic or aromatic amine (RNH<sub>2</sub>). For an aliphatic amine, the reaction is carried out in ethanol; whereas, for an aromatic amine, the reaction is accomplished in benzene with an acid catalyst such as tin tetrachloride. Subsequent reaction of the intermediate beta-amino ester species with the appropriate oxalate diester and the corresponding alkoxide followed by quenching with an acid, preferably HCl, gives the pyrrolidinone 2. The oximes 2' are formed by reaction of 2 with hydroxylamine hydrochloride in pyridine. Hydrogenation of the resulting oxime with palladium on carbon proceeds stereospecifically to give the cis-substituted aminopyrrolidinone 3. N-acylation of 3 with (hetero)arylacids by using one of several common acid-activating reagents [CDI, DCC, SOCl<sub>2</sub>] gives the amide 4 [X is direct bond or CH<sub>2</sub>]. Alternatively, treating 3 with an

appropriate isocyanate or haloformate in the presence of a base such as triethylamine affords the pyrrolidinone urea [X = NH] or urethane [X = O] 4 respectively. Saponification of the ester moiety of 4 (for R<sub>3</sub> = Me, Et) affords the trans-substituted pyrrolidinone carboxylic acid 5. Alternatively ester cleavage of 4 (for R<sub>3</sub> = tert butyl) may be accomplished with an acid, preferably trifluoroacetic acid, affording the cis-substituted pyrrolidinone carboxylic acid 5.

The amides trans-6 and cis-6 are prepared by coupling trans-5 or cis-5, respectively, with an appropriate amine utilizing an acid-activating agent such as carbonyldiimidazole (CDI).

## SCHEME II: SYNTHESIS OF HOMOLOGATED PYRROLIDINONES

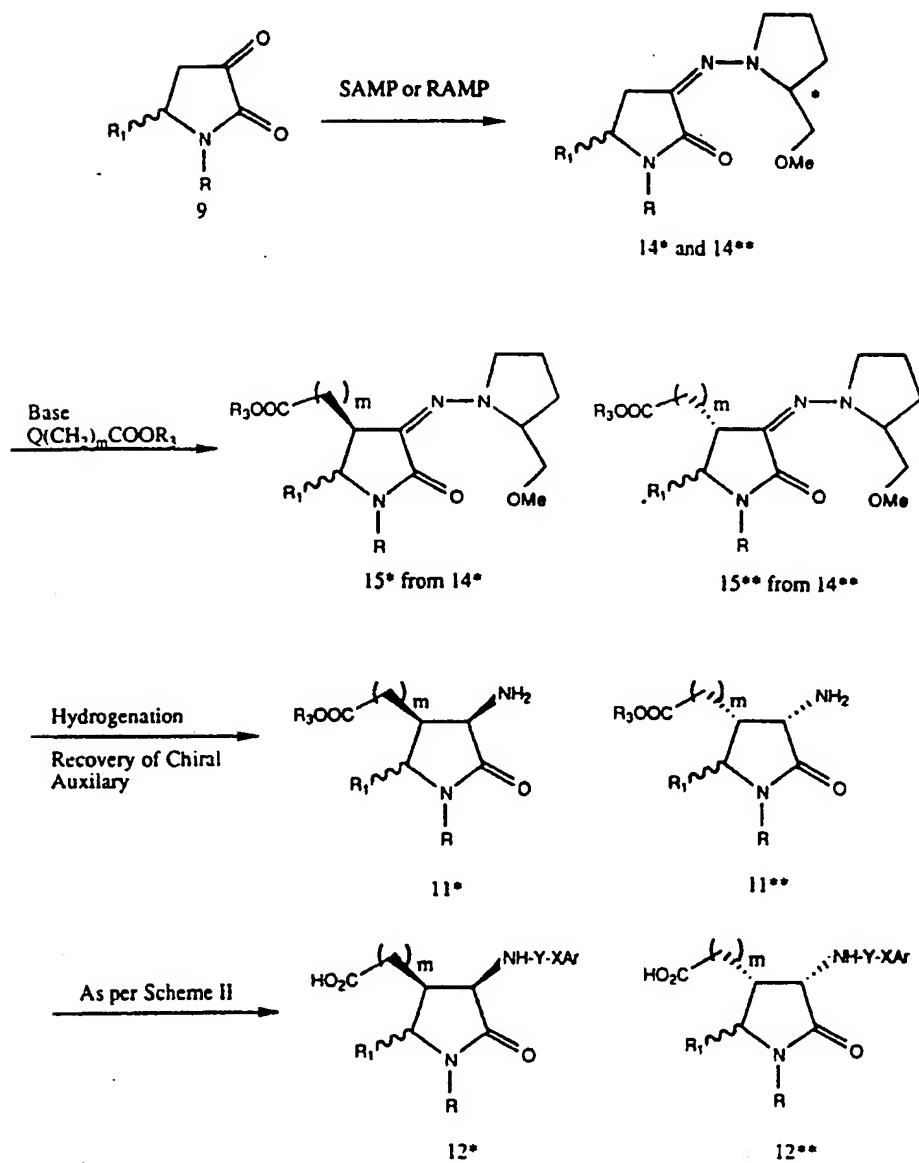




The synthesis of homologated pyrrolidinones ( $m = 1$  to  $3$ ) of Formula I wherein  $R_4$  is hydrogen or alkyl (Scheme II) again relies on methodology reported by Southwick (vide supra) for the preparation of intermediates 9. Hydrolysis and decarboxylation of pyrrolidinone ester 2 proceeds under acidic or basic conditions to give ketopyrrolidinone 9. The ketone 9 may optionally be alkylated in the 4-position ( $R_4$ ) by treatment with a base such as LDA and quenching with an alkylating agent  $R-Q$  such as methyl iodide. Subsequent reaction under basic conditions with an alkylating agent such as ethyl bromoacetate yields the alkylated ketopyrrolidinone 10. Formation of the oxime of ketone 10 with hydroxylamine hydrochloride in pyridine followed by hydrogenation with palladium on carbon affords the aminopyrrolidinone 11. N-acylation of 11 with (hetero)arylacids using above-described acid-activating reagents followed by ester hydrolysis affords the pyrrolidinone amide 12 [ $X$  is direct bond or  $CH_2$ ]. Alternatively, treating 11 with an appropriate isocyanate or an appropriate haloformate in the presence of a base such as triethylamine followed by ester hydrolysis affords the urea 12 [ $X = NH$ ] or urethane 12 [ $X = O$ ], respectively. The amides 13 are prepared by coupling 12 with the appropriate amine

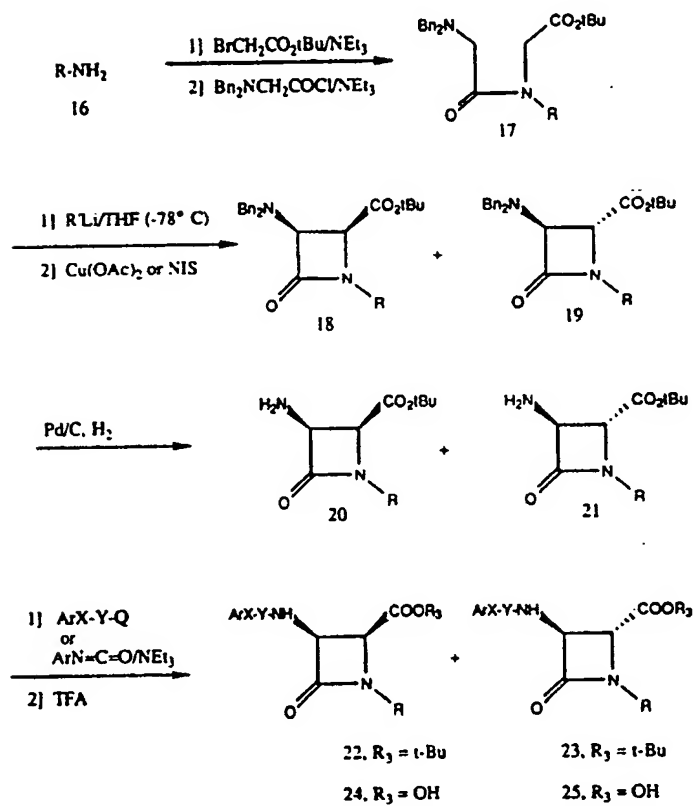
utilizing an acid-activating agent such as  
carbonyldiimidazole (CDI).

SCHEME III: CHIRAL SYNTHESIS OF PYRROLIDINONES  
[\* and \*\* indicate individual isomers]



The synthesis of nonracemic pyrrolidinones of Formula I (Scheme III) utilizes methodology described by Dieter Enders et al. (Org. Syn. 65, 183 (1987)) to form the nonracemic intermediates 11\* and 11\*\*. Thus, reaction of ketopyrrolidinone 9 with commercially-available hydrazines (S)- or (R)-1-amino-2-methoxymethylpyrrolidine (SAMP or RAMP, respectively) in benzene under Dean-Stark conditions affords the corresponding hydrazone 14\* or 14\*\*. Reaction of each hydrazone individually under basic conditions with an electrophile such as ethyl bromoacetate affords alkylated hydrazones 15\* and 15\*\* in high diastereomeric excess. Removal of the hydrazone under hydrogenolysis conditions affords the cis-substituted aminopyrrolidinone 11\* or 11\*\*, depending upon the particular chiral hydrazine used. Coupling of the amines 11\* and 11\*\* followed by ester saponification proceeds as in Scheme II to afford the nonracemic cis-substituted pyrrolidinone 12\* and 12\*\* amides [X is a direct bond or CH<sub>2</sub>], ureas [X = NH], and urethanes [X = O] as described above in Scheme II.

## SCHEME IV: SYNTHESIS OF BETA-LACTAM CCK ANTAGONISTS



The synthesis of  $\beta$ -lactam of Formula I wherein  $n = 0$  (Scheme IV) involves the use of methodology reported by T. Kawabata et al. [J. Amer. Chem. Soc. (1989), 111, 6843 & Tetrahedron Letters (1989), 30, 4837] for the preparation of intermediates 20 and 21. Thus, the appropriate aliphatic or aromatic amine 16 is reacted sequentially with *t*-butylbromoacetate/triethylamine and *N,N*-dibenzylglycine acid chloride/triethylamine to afford the intermediates of general structure 17. Dianion formation with two equivalents of alkyllithium base, followed by treatment with  $\text{Cu}(\text{OAc})_2$ , gives predominantly the *trans*-substituted azetidinone 19. Alternatively, substituting the reagent *N*-iodosuccinimide (NIS) in the second step affords predominately the *cis*-substituted azetidinone 18. When the amine 16 contains a homochiral R group, the azetidinones 18 & 19 may be prepared asymmetrically.

Deprotection of the dibenzylamine moiety by hydrogenolysis gives the 3-aminoazetidinones 20 and 21 from 18 and 19, respectively. *N*-Acylation with (hetero)arylacids by using one of several common acid-activating reagents [CDI, DCC,  $\text{SOCl}_2$ ] affords the corresponding amides 22a or 23a [X is direct bond or  $\text{CH}_2$ ]. Alternatively, treating 20 or 21 with

an appropriate isocyanate affords ureas 22b or 23b [X = NH]. Alternatively, treating 20 or 21 with the appropriate haloformate gives rise to urethanes 22c or 23c [X = O]. Alternatively, treating 20 or 21 with an (hetero)aryl sulfonylchloride in the presence of base such as triethylamine gives sulfonamides of formulae 22 or 23 (Y=SO<sub>2</sub>). Compounds of general formulae 22 and 23 are converted to the carboxylic acids 24 and 25 by treatment with an acid, preferably trifluoroacetic acid.

This invention also relates to a method of treatment and prevention of cholecystokinin (CCK) related disorders of the gastrointestinal, central nervous and appetite regulatory systems of mammals, and more specifically, a method of treatment involving the administration of compounds of Formula I as the active ingredient.

For the treatment and prevention of CCK related disorders compounds of Formula I may be administered orally, topically, parenterally, or by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous

injections, intravenous, intramuscular, intrasternal injection or infusion techniques.

The compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. Therapeutically effective doses of the compounds of the present invention required to prevent or arrest the progress of the medical condition are readily ascertained by one of ordinary skill in the art.

Accordingly, the invention provides a class of novel pharmaceutical compositions comprising one or more compounds of the present invention in association with one or more non-toxic, pharmaceutically acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and if desired other active ingredients. The compounds and composition may for example be administered intravascularly, intraperitoneally, subcutaneously, intramuscularly or topically.



For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit contained in a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. These may with advantage contain an amount of active ingredient from about 1 to 250 mg preferably from about 25 to 150 mg. A suitable daily dose for a mammal may vary widely depending on the condition of the patient and other factors. However, a dose of from about 0.1 to 3000 mg/kg body weight, particularly from about 1 to 100 mg/kg body weight may be appropriate.

The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier. A suitable daily dose is from about 0.1 to 100 mg/kg body weight injected per day in multiple doses depending on the disease being treated. A preferred daily dose would be from about 1 to 30 mg/kg body weight.

The dosage regimen for treating an infectious disease condition with the compounds and/or compositions of this

invention is selected in accordance with a variety of factors, including the type, age, weight, sex and medical condition of the patient; the severity of the infection; the route of administration; and the particular compound employed and thus may vary widely.

For therapeutic purposes, the compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If per os, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulphuric acids, gelatin, acacia, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and thus tableted or encapsulated for convenient administration. Alternatively, the compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art. Appropriate dosages, in any given instance, of course depend upon the nature and severity of

the condition treated, the route of administration, and the species of mammal involved, including its size and any individual idiosyncrasies.

Representative carriers, diluents and adjuvants include for example, water, lactose, gelatin, starches, magnesium stearate, talc, vegetable oils, gums, polyalkylene glycols, petroleum jelly, etc. The pharmaceutical compositions may be made up in a solid form such as granules, powders or suppositories or in a liquid form such as solutions, suspensions or emulsions. The pharmaceutical compositions may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional pharmaceutical adjuvants such as preservatives, stabilizers, wetting agents, emulsifiers, buffers, etc.

Dosage levels of the order from about 0.01 mg to about 10 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (from about 10 mg to about 1000 mg per patient per day).

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form

will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of subjects may contain from 5 mg to 1.0 g of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to 95 percent of the total composition. Dosage unit forms will generally contain between from about 25 mg to about 500 mg of active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The following Examples are intended to further illustrate the present invention and not to limit the invention in spirit or scope. In the Examples, all parts are parts by weight unless otherwise expressly set forth.

## Preparation of Starting Materials

## Example A

## Preparation of

## Ethyl 3-(phenylamino)propanoate

According to the procedure of P. L. Southwick, J. Am. Chem. Soc. 75 3413 (1953), to a solution of aniline (31.86 g, .35 mol) and ethyl acrylate (35.0 g, 0.35 mol) in 200 ml of dry benzene (freshly distilled from  $\text{CaH}_2$ ) was added 0.5 ml of tin tetrachloride and the resulting solution was heated under reflux for 24 h. After cooling to room temperature the suspension was filtered to remove the inorganic solids and then concentrated in vacuo to give a dark green oil which was chromatographed on silica gel eluting with ethyl acetate/toluene (30/70) to give the title compound (40.7 g, 60%) as a light yellow oil. B.p. 95-98°C at 0.1 mm Hg.

## Example B

## Preparation of

## 1,1-Dimethylethyl 3-(phenylamino)propanoate

To a solution of aniline (27.9 g, 0.30 mol) and tert-butyl acrylate (38.4 g, 0.30 mol) in dry benzene (500 ml) was added tin tetrachloride (2 ml) and the resulting solution was heated under reflux for 18 h. The resulting suspension was filtered and the filtrate was concentrated in vacuo giving a residue which was chromatographed on silica gel eluting with 25/75 ethyl acetate/hexane to give the title compound (22.53 g, 34%) as an oil. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.12 (2H, t), 6.71 (1H, m), 6.62 (2H, d), 3.40 (2H, t), 2.54 (2H, t), 1.44 (9H, s).

## Example C

## Preparation of

## 1,1-Dimethylethyl 3-[(2-fluorophenyl)amino]propanoate

To a solution of 2-fluoroaniline (22.06 g, 0.198 mol) and freshly distilled tert-butyl acrylate (25.45 g, 0.198 mol) in dry benzene (250 ml) was added tin tetrachloride (1 ml) and the mixture was refluxed for 60 h. The resulting suspension was filtered and the filtrate was evaporated to give a semisolid which was chromatographed on silica gel eluting with 25/75 ethyl acetate/hexane to give the title compound (5.4 g, 11%). Anal calcd for  $C_{13}H_{18}NO_2F$ : C, 65.25; H, 7.58; N, 5.85. Found: C, 65.49; H, 7.75; N, 5.80. MS M+1 calcd for  $C_{13}H_{18}NO_2F$  240, found 240.

#### Example D

##### Preparation of

Ethyl 2,5-dihydro-4-hydroxy-5-oxo-1-pentyl-1H-pyrrole-3-carboxylate

The title compound was prepared by the general method of Southwick [J. Org. Chem. 21, 1087 (1956)]. Thus to a solution of n-pentylamine (8.04 g, 92.3 mmol) in 50 ml of dry EtOH was added ethyl acrylate (9.24 g, 92.3 mmol) with

stirring under nitrogen at room temperature. After 18 h at room temperature, diethyl oxalate (13.5 g, 92.3 mmol) was added followed by a solution of sodium ethoxide in EtOH [made from sodium (2.12 g, 92.3 mmol) in 50 ml of dry EtOH]. The reaction mixture was then heated under reflux for 1 hour. To the resulting suspension was added 150 ml H<sub>2</sub>O and the reaction mixture was then concentrated under a stream of nitrogen to remove the EtOH. The white solid was then dissolved in 200 ml H<sub>2</sub>O and the solution was acidified with concentrated aqueous HCl (8.9 ml of a 10.4 N solution). The resulting crystals were filtered, washed with water and dried to give the title compound (15.9 g, 71.4%) as colorless plates: mp 122-123°C. Anal calcd for C<sub>12</sub>H<sub>19</sub>NO<sub>4</sub>: C, 59.74; H, 7.94; N, 5.80. Found: C, 59.46; H, 7.87; N, 5.83.



## Example E

## Preparation of

Ethyl 2,5-dihydro-4-hydroxy-5-oxo-1-phenyl-1H-pyrrole-3-carboxylate

The title compound was prepared as described by Southwick in J. Am. Chem. Soc. 75 3413 (1953). Thus to a solution of ethyl 2-phenylaminopropionate (40.7 g, 0.211 mol) and diethyl oxylate (30.8 g, 0.211 mol) in EtOH (250 ml, freshly distilled from Na) cooled to -3°C was added via cannula a solution of sodium ethoxide in EtOH freshly made from 280 ml EtOH and sodium (4.85 g, 0.211 mol). The temperature was maintained below 5°C throughout the addition. After the addition was complete the solution was allowed to warm to room temperature and stirring was continued overnight. The resulting slurry was acidified with 15% HCl to pH = 2 and the resulting precipitate was filtered to give the title compound (29.3 g, 56%) as a colorless powder. Calcd for  $C_{13}H_{13}NO_4$ : C, 63.15; H, 5.30; N, 5.66. Found C, 62.68; H, 5.31; N, 5.55. DSC = 155.98 - 158.33°C at 130.5 J/g.

## Example F

## Preparation of

1,1-Dimethylethyl 2,5-dihydro-4-hydroxy-5-oxo-1-pentyl-1H-pyrrole-3-carboxylate

To a solution of n-pentyl amine (21.72 g, 0.25 mol) in 110 ml of EtOH (freshly distilled from sodium) was added tert-butyl acrylate (36.62 ml, 0.26 mol) via syringe and the resulting solution was stirred under an atmosphere of argon for 12 h at room temperature. To the solution was then added diethyl oxalate (36.54 g, 0.25 mol). The solution was then cooled to 0°C and a freshly prepared solution of sodium ethoxide (from 5.75 g (.25 mole) of sodium and 75 ml of EtOH) was added via cannula while maintaining the temperature between 0°C and 5°C. After the addition was complete, the solution was allowed to warm to room temperature and stirred overnight. To the resulting slurry was added 400 ml of water followed the slow addition of 30% aqueous HCl to acidify to pH=4. The suspension was then extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic phase was dried over MgSO<sub>4</sub>, filtered, and concentrated in vacuo to give a white solid. Recrystallization from ethyl acetate

gave the title compound (31.57 g, 47%) as a colorless powder.

Anal calcd for  $C_{14}H_{23}NO_4 \cdot 1/4H_2O$ : C, 61.40; H, 8.65; N, 5.11.

Found: C, 61.38; H, 8.54; N, 5.22. MS M+1 calcd for  $C_{14}H_{23}NO_4$ , 270, found 270. DSC = 102.3-106.4°C at 101.7 J/g.

Chromatography of the mother liquor on silica gel eluting with EtOH/ $CH_2Cl_2$ /HOAc (2/98/1) gave an additional 17.5 g (26%) of the title compound.

#### Example G

##### Preparation of

##### 1,1-Dimethylethyl 2,5-dihydro-4-hydroxy-5-oxo-1-phenyl-1H-pyrrole-3-carboxylate

To a solution of the title compound of Example B (29.37 g, 0.133 mol) and di-tert-butyl oxalate (26.90 g, 0.133 mol) in dry THF (350 ml) was added potassium tert-butoxide (29.84 g, 0.266 mol) and the resulting solution was heated under reflux for 24 h. The mixture was then cooled and the solvent removed in vacuo. The resulting solid was suspended in  $CH_2Cl_2$  and 1N aqueous HCl was added. The resulting suspension was filtered and the organic filtrate was dried over  $MgSO_4$  and

concentrated in vacuo. The residue was then chromatographed on silica gel eluting with 1/1/98 HOAc/EtOH/CH<sub>2</sub>Cl<sub>2</sub> to give the title compound (19.06 g, 52%) as a solid. Anal calcd for C<sub>15</sub>H<sub>17</sub>NO<sub>4</sub>: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.05; H, 6.33; N, 4.86. MS M+1 calcd for C<sub>15</sub>H<sub>17</sub>NO<sub>4</sub> 276, found 276.

#### Example H

##### Preparation of

1,1-Dimethylethyl 1-(2-fluorophenyl)-2,5-dihydro-4-hydroxy-5-oxo-1H-pyrrole-3-carboxylate

To a solution of the title compound of Example C (5.41 g, 22.6 mmol) in dry THF (100 ml) was added di-tert-butyl oxalate (4.57 g, 22.6 mmol), followed by potassium tert-butoxide (5.07 g, 45.2 mmol) and the resulting dark yellow solution was stirred for 84 h at room temperature. The reaction mixture was then acidified with 1 N HCl to pH = 3, followed by the addition of H<sub>2</sub>O (35 ml) and the mixture was then extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were dried with MgSO<sub>4</sub>, filtered and dried to give a solid which was chromatographed on silica gel eluting with 1/1/98

MeOH/HOAc/CH<sub>2</sub>Cl<sub>2</sub> to give the title compound (3.166 g, 48%).

Anal calcd for C<sub>15</sub>H<sub>16</sub>NO<sub>4</sub>F: C, 61.43; H, 5.50; N, 4.78. Found: C, 61.16; H, 5.50; N, 4.77.

#### Example I

##### Preparation of

1,1-Dimethylethyl 2,5-dihydro-4-hydroxy-5-oxo-1-(phenylmethyl)-1H-pyrrole-3-carboxylate

To a solution of benzyl amine (7.3 ml, 0.067 mol) in dry EtOH (freshly distilled from sodium) was added tert-butyl acrylate (6.8 ml, 0.046 mol) via syringe and the resulting solution was stirred under an atmosphere of argon for 64 h at room temperature. To the solution was then added diethyl oxalate (9.90 g, 0.068 mol). The solution was then cooled to 0°C and a freshly prepared solution of sodium ethoxide [freshly prepared from sodium (1.7 g, 0.074 mol) and 75 ml of EtOH] was added via cannula while maintaining the temperature between 0°C and 5°C. After the addition was complete the solution was warmed to room temperature and stirred overnight. To the resulting slurry was added 100 ml of water

followed by the slow addition of 30% aqueous HCl to acidify to pH = 1. The suspension was then extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic phase was dried over MgSO<sub>4</sub>, filtered, and concentrated in vacuo to give the title compound as a light pink powder (8.37 g, 62.9%). Purification of an analytical sample by chromatography on silica gel eluting with 5/94.5/0.5 MeOH/CH<sub>2</sub>Cl<sub>2</sub>/HOAc gave 8.67g, (65%) of the title compound as a powder. Anal calcd for C<sub>16</sub>H<sub>19</sub>NO<sub>4</sub>: C, 66.43; H, 6.52; N, 4.84. Found: C, 66.38; H, 6.70; N, 5.10. DSC = 172.2-176.2° at 190.9 J/g.

#### Example J

##### Preparation of

Ethyl 2,5-dihydro-4-hydroxy-2-methyl-5-oxo-1-pentyl-1H-pyrrole-3-carboxylate

To a solution of n-pentyl amine (28.98 ml, 0.25 mol) in absolute EtOH (110 ml) was added ethyl crotonate (31.1 ml, 0.25 mol) and the solution was stirred for 16 h at room temperature. To the clear solution was then added diethyl oxalate (33.95 ml, 0.25 mol) followed by a solution of sodium

ethoxide [freshly prepared from sodium (5.75 g, 0.25 mol) and 75 ml of absolute EtOH]. After stirring for 16 h at room temperature, the solvent was removed in vacuo to give an orange oil. Water was added to the oil followed by 1 N HCl to acidify to pH = 3, and the mixture was then extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 X 500 ml). The combined organic layers were washed with water and brine and then concentrated in vacuo to give an oil which was chromatographed on silica gel eluting with 10/89/1 EtOH/CH<sub>2</sub>Cl<sub>2</sub>/HOAc to give the title compound (21.88 g, 34%) as a pink solid. DSC = 37.8-44.3°C at 63.9 J/g.

#### Example K

##### Preparation of

Ethyl 4-(hydroxyimino)-5-oxo-1-pentyl-3-pyrrolidine-carboxylate

To a solution of the title compound of Example D (5.0 g, 20.2 mmol) in 50 ml of pyridine was added hydroxylamine hydrochloride (1.58 g, 24.2 mmol) and the solution was stirred for 16 h at room temperature. Concentration in vacuo gave an oil which was chromatographed on silica gel eluting

with EtOH/CH<sub>2</sub>Cl<sub>2</sub> (10/90) to give the title compound (5.18 g, 98%) as a colorless solid. MS calcd for C<sub>12</sub>H<sub>20</sub>N<sub>2</sub>O<sub>4</sub> 256, found 256.

#### Example L

##### Preparation of

Ethyl 4-(hydroxyimino)-5-oxo-1-phenyl-3-pyrrolidine-carboxylate

To a mechanically stirred solution of the title compound of Example E (21 g, 0.085 mol) in 450 ml of pyridine was added hydroxylamine hydrochloride (8.83 g, 0.127 mol). After stirring for 4 days at room temperature the solution was concentrated in vacuo to give a solid which was chromatographed on silica gel eluting with 3% EtOH/CH<sub>2</sub>Cl<sub>2</sub> to give the title compound (13.71 g, 61%) as a colorless powder: Anal calcd for C<sub>13</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub>: C, 59.53; H, 5.40; N, 10.68. Found: C, 59.48; H, 5.47; N, 10.64. MS calcd for C<sub>13</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub> 262, found 262. DSC = 153.2-155.4°C at 91.1 J/g.



## Example M

## Preparation of

1,1-Dimethylethyl 4-(hydroxyimino)-5-oxo-1-pentyl-3-pyrrolidine carboxylate

To a mechanically stirred solution of the title compound of Example F (17.5 g, 0.065 mol) in 60 ml of pyridine was added hydroxylamine hydrochloride (5.41 g, 0.078 mol) and resulting solution was stirred for 36 h. Evaporation of the solvent afforded a light yellow oil which was chromatographed on silica gel eluting with 3% EtOH/CH<sub>2</sub>Cl<sub>2</sub> to give the title compound (16.48 g, 89%) as a white solid: Anal calcd for C<sub>14</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub>: C, 59.14, H, 8.51; N, 9.85. Found C, 58.91; H, 8.48; N, 9.71. MS calcd for C<sub>14</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub>, 284, found 284. DSC = 131.0-134.7°C at 93.1 J/g.

## Example N

## Preparation of

1,1-Dimethylethyl 4-(hydroxyimino)-5-oxo-1-phenyl-3-pyrrolidine carboxylate

To a solution of the title compound of Example G (9.2 g, 0.033 mol) in pyridine (100 ml) was added hydroxylamine hydrochloride (11.62 g, 0.167 mol) and the resulting solution was stirred at room temperature for 4 days. Concentration in vacuo gave a solid which was purified on a Waters Prep 500A eluting with 5/95 EtOH/CH<sub>2</sub>Cl<sub>2</sub> to afford the title compound (3.08 g, 32%) as a solid. DSC = 187.8-190.8°C at 378.5 J/g.

## Example O

## Preparation of

1,1-Dimethylethyl 1-(2-fluorophenyl)-4-(hydroxyimino)-5-oxo-3-pyrrolidinecarboxylate

To a solution of the title compound of Example H (3.16 g, 10.8 mmol) in pyridine (50 ml) was added hydroxylamine hydrochloride (3.73 g, 54. mmol) and the reaction was stirred for 5 days(d) at room temperature. After the reaction was concentrated in vacuo, H<sub>2</sub>O was added and the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>. Drying of the organic phase (MgSO<sub>4</sub>) and concentration gave a solid which was chromatographed on silica gel eluting with 2% EtOH/CH<sub>2</sub>Cl<sub>2</sub> to give the title compound (1.91 g, 57%). Anal calcd for C<sub>15</sub>H<sub>17</sub>N<sub>2</sub>O<sub>4</sub>F: C, 58.44; H, 5.56; N, 9.09. Found: C, 58.43; H, 5.62; N, 8.75. DSC = 175.1-180.2°C at 225.6 J/g.

#### Example P

##### Preparation of

1,1-Dimethylethyl 4-(hydroxyimino)-5-oxo-1-(phenylmethyl)-3-pyrrolidinecarboxylate

To a solution of the title compound of Example I (8.07 g, 27.9 mmol) in 150 ml of pyridine was added hydroxylamine hydrochloride (9.69 g, 139 mmol) and resulting solution was stirred for 4 d. Addition of H<sub>2</sub>O resulted in the formation

of precipitate which was filtered to give the title compound (7.11 g, 84%) as a colorless solid. Calculated for  $C_{16}H_{20}N_2O_4 \cdot 1/2H_2O$ : C, 61.35; H, 6.76; N, 8.94. Found C, 61.35; H, 6.57, N, 9.34.

#### Example Q

##### Preparation of

Ethyl 4-(hydroxyimino)-2-methyl-5-oxo-1-pentyl-3-pyrrolidinecarboxylate

To the title compound of Example J (21.6 g, 0.085 mol) in pyridine (150 ml) was added hydroxylamine hydrochloride (10.6 g, 0.17 mol) and the solution was stirred for 5 days. The solvent was removed in vacuo to give an orange oil which was chromatographed on silica gel eluting with 2% EtOH/ $CH_2Cl_2$  to give the title compound (13.67 g, 59%) as an oil. Calculated  $C_{13}H_{22}N_2O_4 \cdot 1/2H_2O$ : C, 55.90; H, 8.30; N, 10.02. Found: C, 55.99; H, 8.38; N, 10.00. MS calcd for  $C_{13}H_{22}N_2O_4$ , 270, found 270.

## Example R

## Preparation of

## Ethyl 4-amino-5-oxo-1-pentyl-3-pyrrolidinecarboxylate

A solution of the title compound of Example K (1.0 g, 3.9 mmol) in 50 ml EtOH was hydrogenated with 10% palladium on carbon at 60 psi at 60°C for 18 h. Filtration and evaporation of the solvent gave an oil which was chromatographed on silica gel eluting with EtOH/CH<sub>2</sub>Cl<sub>2</sub> (5/95) to give the title compound (382 mg, 40%) as a colorless solid. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 4.20 (2H, q), 3.80 (1H, d), 3.59 (1H, td), 3.48 (1H, q), 3.35 (1H, m), 3.29 (2H, m), 1.69 (2H, br s), 1.52 (2H, m), 1.32 (4H, m), 1.30 (3H, t), 0.90 (3H, t).

## Example S

## Preparation of

## Ethyl 4-amino-5-oxo-1-phenyl-3-pyrrolidinecarboxylate

A solution of oxime of Example L (791 mg, 3.01 mmol) in 50 ml of EtOH was hydrogenated with Raney nickel in a 150 ml Parr bomb with 1,000 psi of hydrogen at 50°C for 4h. The solution was then filtered to remove the catalyst and the solution was concentrated in vacuo. The resulting oil was radially chromatographed on silica gel eluting with 7% EtOH/CH<sub>2</sub>Cl<sub>2</sub> to give the title compound (342 mg, 44%). DSC = 190.3-193.8°C at 71.1 J/g.

## Example T

## Preparation of

## 1,1-Dimethylethyl 4-amino-5-oxo-1-pentyl-3-pyrrolidine-carboxylate

A solution of oxime of Example M (20.0 g, 68.6 mmol) in 200 ml of EtOH was hydrogenated with 10% palladium on carbon at 1200 psi at 70°C for 24 h. Filtration and evaporation of the solution gave the title compound (18.5 g, 100%) as colorless, low-melting solid. MS calcd for  $C_{14}H_{26}N_2O_3$  270, found 270.  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  3.63 (1H, d), 3.50 (1H, m), 3.41 (1H, m), 3.25 (2H, m), 1.72 (2H, s), 1.52 (1H, m), 1.47 (9H, s), 1.29 (4H, m), 0.89 (2H, t).

#### Example V

##### Preparation of

##### 1,1-Dimethylethyl 4-amino-5-oxo-1-phenyl-3-pyrrolidine-carboxylate

A solution of oxime of Example N (3.08 g, 10.6 mmol) in EtOH (80 ml) was hydrogenated at 1000 psi at 70°C on 10% palladium on carbon. Filtration and concentration of the filtrate gave an oil which was chromatographed on silica gel eluting with 2/97.75/0.25 EtOH/ $CH_2Cl_2$ / $NH_4OH$  to afford the title compound (1.76 g, 60%) as a white solid. Anal calcd for  $C_{15}H_{20}N_2O_3$ : C, 65.20; H, 7.30; N, 10.14. Found: C, 64.95; H, 7.39; N,

10.04. MS calcd for  $C_{15}H_{20}N_2O_3$ , 276, found 276. DSC = 105.0-121.1° at 57.2 J/g.

#### Example W

##### Preparation of

1,1-Dimethylethyl 4-amino-1-(2-fluorophenyl)-5-oxo-3-pyrrolidinecarboxylate

A solution of oxime of Example O (1.23 g, 3.99 mmol) in EtOH was hydrogenated at 1000 psi on Pd/C at 70°C for 24 h. The solvent was removed in vacuo to give an oil which was chromatographed on silica gel eluting with 2% EtOH/ $CH_2Cl_2$  to give the title compound (850 mg, 72%) as a solid. Anal calcd for  $C_{15}H_{19}N_2O_3F$ : C, 61.21; H, 6.51; N, 9.52; F, 6.45. Found: C, 60.87; H, 6.61; N, 9.32; F, 6.10. MS calcd for  $C_{15}H_{19}N_2O_3F$  294, found 294. DSC = 71.2-74.9°C at 76.6 J/g.

#### Example X

##### Preparation of



1,1-Dimethylethyl 4-amino-5-oxo-1-(phenylmethyl)-3-pyrrolidinecarboxylate

A solution of 2.014g (6.6 mmol) of the oxime of Example P in EtOH (400 ml) was hydrogenated with 4% palladium on carbon at 1000 psi at 70°C for 24 h. Filtration and evaporation of the filtrate gave a white solid which was chromatographed on silica gel eluting with 3% CH<sub>3</sub>OH/CH<sub>2</sub>Cl<sub>2</sub>/1% NH<sub>4</sub>OH to give the title compound (997 mg, 52%). Anal. calcd. for C<sub>16</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub>·1/2H<sub>2</sub>O: C, 64.19; H, 7.74; N, 9.36 Found: C, 64.36; H, 7.71; N, 9.41.

Example Y

Preparation of

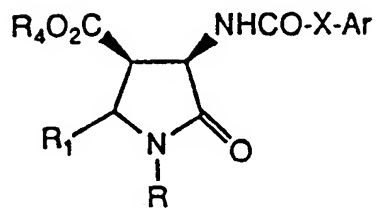
Ethyl 4-amino-2-methyl-5-oxo-1-pentyl-3-pyrrolidinecarboxylate

A solution of oxime of Example Q in EtOH is hydrogenated with 10% palladium on carbon at 1200 psi at 70°C for 24 h. Filtration and evaporation of the filtrate gives a residue

which is chromatographed on silica gel eluting with 2% EtOH/CH<sub>2</sub>Cl<sub>2</sub>, to give the title compound.

TABLE A

Examples 1 to 26 Have The Following Structures



Ex	R	R <sub>1</sub>	R <sub>4</sub>	X	Ar
1	n-pentyl	H	Et	bond	3-quinoliny
2	phenyl	H	t-Bu	bond	"
3	2-F-phenyl	H	t-Bu	bond	"
4	phenyl	H	Et	bond	2-indolyl
5	phenyl	H	t-Bu	bond	"
6	benzyl	H	t-Bu	bond	"
7	n-pentyl	Me	Et	bond	"
8	phenyl	H	Et	CH <sub>2</sub>	3-indolyl
9	pentyl	H	t-Bu	bond	3,4-dichlorophenyl
10	pentyl	H	t-Bu	NH	"
11	phenyl	H	Et	bond	"
12	phenyl	H	Et	NH	"
13	phenyl	H	t-Bu	O	"
14	benzyl	H	t-Bu	bond	"
15	benzyl	H	t-Bu	NH	"
16	n-pentyl	H	Et	bond	2-naphthyl
17	n-pentyl	H	t-Bu	NH	"
18	phenyl	H	Et	bond	"
19	phenyl	H	t-Bu	bond	"

<u>Ex</u>	<u>R</u>	<u>R<sub>1</sub></u>	<u>R<sub>2</sub></u>	<u>X</u>	<u>Ar</u>
20	2-F-phenyl	H	t-Bu	bond	"
21	benzyl	H	t-Bu	bond	"
22	n-pentyl	H	t-Bu	bond	4-chlorophenyl
23	phenyl	H	Et	bond	"
24	n-pentyl	H	Et	NH	"
25	phenyl	H	t-Bu	bond	3-indazolyl
26	phenyl	H	t-Bu	bond	2-pyrazinyl

## Example 1

## Preparation of

Ethyl cis-5-oxo-1-pentyl-4-[(3-quinolinylcarbonyl)amino]-3-pyrrolidinecarboxylate

To quinoline-3-carboxylic acid (100 mg, 0.578 mmol) suspended in  $\text{CH}_2\text{Cl}_2$ , was added 2 drops of dimethylformamide followed by the dropwise addition of oxalyl chloride (0.1 ml, 1.15 mmol). After stirring for 2 h at room temperature the solution was evaporated to dryness to give the acid chloride. The acid chloride was then redissolved in  $\text{CH}_2\text{Cl}_2$ , and syringed dropwise into a solution of the aminopyrrolidinone of Example R (140 mg, 0.578 mmol) with triethylamine (0.4 ml, 2.89 mmol) in  $\text{CH}_2\text{Cl}_2$ . After stirring for 12 h at room temperature the reaction mixture was evaporated in vacuo to give an oil which was chromatographed on silica gel eluting with  $\text{EtOH}/\text{CH}_2\text{Cl}_2$  (2%-5%) to give the title compound (173 mg, 75%) as a colorless solid. MS calcd for  $\text{C}_{22}\text{H}_{27}\text{N}_3\text{O}_4$ , 397, found 397.

## Example 2

## Preparation of

1,1-Dimethylethyl cis-5-oxo-1-phenyl-4-[(3-quinolinylcarbonyl)amino]-3-pyrrolidinecarboxylate

To a solution of 3-quinolinecarboxylic acid (118 mg, 0.68 mmol) in  $\text{CH}_2\text{Cl}_2$  (3 ml) was added oxalyl chloride (0.12 ml, 1.36 mmol) and the resulting solution was stirred for 2.5 h at room temperature. The solvent was removed in vacuo and the acid chloride was redissolved in  $\text{CH}_2\text{Cl}_2$  (3 ml) to which was added the aminopyrrolidinone of Example V (200 mg, 0.68 mmol) and triethylamine (344 mg, 3.4 mmol) in  $\text{CH}_2\text{Cl}_2$  (3 ml). After stirring for 18 h at room temperature, the solvent was removed in vacuo and the resulting oil was purified by radial chromatography on a silica gel plate eluting with 2%  $\text{EtOH}/\text{CH}_2\text{Cl}_2$  to give the title compound (223 mg, 73%) as a solid.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  9.38 (1H, d), 8.68 (1H, d), 8.18 (1H, d), 7.94 (1H, d), 7.85 (1H, t), 7.64 (2H, d), 7.58 (1H, m), 7.42 (2H, t), 7.21 (1H, t), 5.23 (1H, t), 4.15 (1H, m), 4.06 (1H, d), 3.81 (1H, t), 1.38 (9H, s).

## Example 3

## Preparation of

1,1-Dimethylethyl cis-1-(2-fluorophenyl)-5-oxo-4-[(3-quinolinylcarbonyl)amino]-3-pyrrolidinecarboxylate

To a solution of 3-quinolinecarboxylic acid (118 mg, 0.68 mmol) in  $\text{CH}_2\text{Cl}_2$  (3 ml) was added oxalyl chloride (0.12 ml, 1.36 mmol) and the solution was stirred for 2.5 h. Removal of the solvent in vacuo gave a colorless solid which was redissolved in  $\text{CH}_2\text{Cl}_2$  (3 ml). To this solution was added a solution of aminopyrrolidinone of Example W (200 mg, 0.68 mmol) and triethylamine (344 mg, 3.4 mmol) in  $\text{CH}_2\text{Cl}_2$  (3 ml) and the resulting solution was stirred for 18 h. Removal of the solvent in vacuo and purification of the resulting solid via radial chromatography (4 mm plate) eluting with 2% EtOH/ $\text{CH}_2\text{Cl}_2$  gave the title compound (223 mg, 73%) as a solid.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  9.35 (1H, d), 8.68 (1H, d), 8.19 (1H, d), 7.94 (1H, d), 7.84 (1H t), 7.64 (1H, t), 7.54 (1H, t), 7.32 (1H, m), 7.19 (2H, m), 5.28 (1H, t), 4.21 (1H, m), 3.91 (1H, d), 3.78 (1H, q), 3.49 (1H, s), 1.41 (9H, s).

## Example 4

## Preparation of

Ethyl cis-4-[(1H-indol-2-ylcarbonyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylate

To indole-2-carboxylic acid (65 mg, 0.4 mmol) suspended in  $\text{CH}_2\text{Cl}_2$ , was added 2 drops of dimethylformamide followed by the dropwise addition of oxalyl chloride (0.07 ml, 0.8 mmol). After stirring for 2 h at room temperature the solution was evaporated to dryness to give the acid chloride. The acid chloride was then redissolved in  $\text{CH}_2\text{Cl}_2$  and syringed dropwise into a solution of the aminopyrrolidinone of Example S (100 mg, 0.4 mmol) with triethylamine (0.3 ml, 2.0 mmol) in  $\text{CH}_2\text{Cl}_2$ . After stirring for 12 h at room temperature the reaction mixture was evaporated in vacuo to give an oil which was chromatographed on silica gel eluting with  $\text{EtOH}/\text{CH}_2\text{Cl}_2$  2%-5% to give the title compound (68 mg, 43%) as a colorless solid.  $^1\text{NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  9.09 (1H, br s), 7.66 (4H, m), 7.43 (4H, t), 7.16 (1H, m), 6.99 (2H, m), 5.21 (1H, t), 4.14 (4H, m), 4.05 (1H, m), 3.85 (1H, t), 1.14 (3H, t).



## Example 5

## Preparation of

1,1-Dimethylethyl cis-4-[(1H-indol-2-ylcarbonyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylate

To a solution of indole-2-carboxylic acid (103 mg, 0.64 mmol) in dry DMF (1.5 ml) was added 1,1-carbonyldiimidazole (104 mg, 0.64 mmol) and the resulting solution was stirred for 2.5 h at room temperature. To this mixture was then added a solution of aminopyrrolidinone of Example V (177 mg, 0.64 mmol) in dry DMF (1.5 ml). This solution was then stirred for 18 h at room temperature after which time the solvent was removed in vacuo giving an oil. Chromatography of the oil on a silica gel chromatotron plate (2 mm) eluting with 2/98 EtOH/CH<sub>2</sub>Cl<sub>2</sub> gave the title compound (110 mg, 49%) as a solid. <sup>1</sup>NMR (300 MHz, CDCl<sub>3</sub>) δ 9.17 (1H, s), 7.66 (2H, m), 7.43 (2H, t), 7.32 (1H, t), 7.16 (2H, m), 6.98 (2H, m), 5.18 (1H, q), 4.42 (1H, m), 4.10 (2H, m), 3.76 (1H, t), 1.36 (9H, s).

## Example 6

## Preparation of

1,1-Dimethylethyl cis-4-[(1H-indol-2-ylcarbonyl)amino]-5-oxo-1-phenylmethyl)-3-pyrrolidinecarboxylate

To a solution of indole-2-carboxylic acid (183 mg, 1.1 mmol) in DMF was added 1,1-carbonyldiimidazole (84 mg, 1.1 mmol). After stirring for 5 h at room temperature a solution of the aminopyrrolidinone of Example X (330 mg 1.1 mmol) in DMF was added. After stirring for 12 h at room temperature the reaction mixture was evaporated in vacuo to give an oil which was chromatographed on silica gel eluting with EtOH/CH<sub>2</sub>Cl<sub>2</sub> (2%-5%) to give 350 mg (73%) of the title compound.

MS calcd for C<sub>33</sub>H<sub>27</sub>N<sub>3</sub>O<sub>4</sub> 433, found 433.

DSC = 206.10 - 211.61°C at 90.50 J/g

217.23°C at 63.56 J/g.

## Example 7

## Preparation of

Ethyl cis-4-[(1H-indol-2-ylcarbonyl)amino]-2-methyl-5-oxo-1-pentyl-3-pyrrolidinecarboxylate

To indole-2-carboxylic acid (.264 mg, 1.6 mmol) in DMF (3 ml.) was added 1,1-carbonyldiimidazole (260 mg, 1.6 mmol). After stirring for 4 h at room temperature a solution of the aminopyrrolidinone of Example Y (408 mg, 1.6 mmol) in DMF was added. After stirring for 24 h at room temperature the reaction mixture was evaporated in vacuo to give an oil which was chromatographed on silica gel eluting with EtOH/CH<sub>2</sub>Cl<sub>2</sub> (2%-5%) to give the title compound, 600 mg (95%).

<sup>1</sup>NMR (300 MHz, CDCl<sub>3</sub>) δ 0.98 (t, 3H), 3.75 (m, 1H), 3.96 (m, 1H), 4.02 (m, 2H), 4.19 (m, 1H), 5.15 (t, 1H), 7.04 (t, 1H), 7.27 (m, 2H), 7.43 (t, 2H), 7.61 (d, 1H), 7.72 (d, 1H), 8.99 (d, 1H).

## Example 8

## Preparation of

Ethyl cis-4-[(1H-indol-3-ylacetyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylate

To a solution of indole-3-acetic acid (248 mg, 1.42 mmol) in DMF (3 ml) was added 1,1-carboxyldiimidazole (230 mg, 1.42 mmol). After stirring for 2 h a solution of the aminopyrrolidinone of Example S (352 mg, 1.42 mmol) in DMF (1 ml) was added. After stirring for an additional 18 h the solvent was evaporated to give an oil which was chromatographed on silica gel eluting with EtOH/CH<sub>2</sub>Cl<sub>2</sub> (2%-5%) to give 470 mg (91%) of the title compound as a solid.

NMR (DMSO) 400 MHz: 3.25δ, m, 1H; 3.59δ, d, 2H; 3.88δ, t, 1H; 4.01δ, t, 1H; 4.65δ, q, 1H; 6.98δ, t, 1H; 7.08δ, t, 1H; 7.15δ, t, 1H; 7.24δ, d, 1H; 7.37, m, 3H; 7.56δ, d, 1H; 7.78δ, d, 2H; 8.62δ, d, 1H.

## Example 9

## Preparation of

1,1-Dimethylethyl cis-4-[[ (3,4-dichlorophenyl)carbonyl] amino]-5-oxo-1-pentyl-3-pyrrolidinecarboxylate

To a solution of the aminopyrrolidinone of Example T (110 mg, 0.407 mmol) and triethylamine (0.11 ml, 0.814 mmol) in  $\text{CH}_2\text{Cl}_2$  was added a solution of 3,4-dichlorobenzoyl chloride (85 mg, 0.407 mmol) in  $\text{CH}_2\text{Cl}_2$  dropwise via syringe. After stirring for 12 h at room temperature the reaction mixture was evaporated in vacuo to give an oil which was chromatographed on silica gel eluting with  $\text{EtOH}/\text{CH}_2\text{Cl}_2$  (2%-5%) to give the title compound (150 mg, 85%) as a colorless solid. DSC = 108.1-111.3 at 38.5 J/g. Anal calcd for  $\text{C}_{21}\text{H}_{28}\text{N}_2\text{O}_4\text{Cl}_2$ : C, 56.89; H, 6.36; N, 6.32. Found C, 57.09; H, 5.87; N, 6.22. MS calcd for  $\text{C}_{21}\text{H}_{28}\text{N}_2\text{O}_4\text{Cl}_2$  443, found 443.

## Example 10

## Preparation of

1,1-Dimethylethyl cis-4-[[[(3,4-dichlorophenyl)amino]  
carbonyl]amino]-5-oxo-1-pentyl-3-pyrrolidinecarboxylate

To a solution of 3,4-dichlorophenyl isocyanate (76 mg, 0.407 mmol) dissolved in 3 ml of  $\text{CH}_2\text{Cl}_2$  was added a solution of aminopyrrolidinone of Example T (110 mg, 0.407 mmol) in 3 ml of  $\text{CH}_2\text{Cl}_2$  and the resulting solution was stirred for 16 h at room temperature. Evaporation of the solvent in vacuo gave a solid which was purified on silica gel eluting with 5/95 EtOH/ $\text{CH}_2\text{Cl}_2$  to give the title compound (167 mg, 90%) as a colorless solid. DSC = 162.0-164.2°C at 65.0 J/g. MS calculated for  $\text{C}_{21}\text{H}_{29}\text{N}_3\text{O}_4\text{Cl}_2$  458, found 458.

## Example 11

## Preparation of

Ethyl cis-4-[(3,4-dichlorophenyl)carbonyl]amino]-  
5-oxo-1-phenyl-3-pyrrolidinecarboxylate

To a solution of 3,4-dichlorobenzoyl chloride (295 mg, 1.41 mmol) in  $\text{CH}_2\text{Cl}_2$  (4 ml) was added a solution of aminopyrrolidinone of Example S (350 mg, 1.41 mmol) and triethylamine (0.4 ml, 2.82 mmol) in  $\text{CH}_2\text{Cl}_2$  (4 ml) and the resulting solution was stirred for 18 h at room temperature. Concentration in vacuo gave an oil which was chromatographed on silica gel eluting with 2% EtOH/ $\text{CH}_2\text{Cl}_2$  to give the title compound (400 mg, 67%) as a colorless solid. Anal calcd for  $\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_4\text{Cl}_2$ : C, 57.02; H, 4.31; N, 6.65. Found: C, 57.05; H, 4.39; N, 6.50. MS  $\text{M}+1$  calcd for  $\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_4\text{Cl}_2$  422, found 422. DSC = 185.5-193.1°C at 82.8 J/g.

## Example 12

## Preparation of

Ethyl cis-4-[[[(3,4-dichlorophenyl)amino]carbonyl]amino]-  
5-oxo-1-phenyl-3-pyrrolidinecarboxylate

To a solution of 3,4-dichlorophenylisocyanate in  $\text{CH}_2\text{Cl}_2$  (3 ml) was added a solution of aminopyrrolidinone of Example S (350 mg, 1.41 mmol) in  $\text{CH}_2\text{Cl}_2$  (3 ml) and the resulting solution was stirred for 18 h at room temperature. Concentration in vacuo gave a solid which was triturated with  $\text{CH}_2\text{Cl}_2$  and filtered to give the title compound (420 mg, 68%) as a solid. MS  $M+1$  calcd for  $\text{C}_{20}\text{H}_{19}\text{N}_3\text{O}_4\text{Cl}_2$  437, found 437. DSC = 249.1-251.7°C at 112.7 J/g.



## Example 13

## Preparation of

1,1-Dimethylethyl cis-4-[[ (3,4-dichlorophenoxy) carbonyl] amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylate

To a cooled (0°C) solution of aminopyrrolidinone of Example V (300 mg, 1.09 mmol) and triethylamine (0.15 mL, 1.09 mmol) in CH<sub>2</sub>Cl<sub>2</sub> is added 3,4-dichlorophenyl chloroformate (207 mg, 1.09 mmol). After warming to room temperature the reaction is stirred for 12 h. The reaction mixture is then washed with water and brine, dried (MgSO<sub>4</sub>) and concentrated in vacuo to give a residue which is chromatographed on silica gel eluting with EtOH/CH<sub>2</sub>Cl<sub>2</sub> (2%-5%) to give the title compound.

## Example 14

## Preparation of

1,1,-Dimethylethyl cis-4-

[[ (3,4dichlorophenyl)carbonyl]amino]-5-oxo-1-phenylmethyl-3-pyrrolidinecarboxylate

To a solution of 3,4 dichlorobenzoyl chloride (419 mg, 2.0 mmol) in  $\text{CH}_2\text{Cl}_2$  (3 ml) was added a solution of aminopyrrolidinone of Example X (286 mg, .99 mmol) and triethylamine (.28 ml, 2.0 mmol) in  $\text{CH}_2\text{Cl}_2$  (3 ml). After stirring for 18 h at room temperature the reaction mixture was evaporated in vacuo to give a solid which was chromatographed on silica gel eluting with 2% EtOH/ $\text{CH}_2\text{Cl}_2$  to give 352 mg (77%) of the title compound.

Anal calcd for  $\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_4\text{Cl}_2$ : C, 59.62; H, 5.22; N, 6.05.

Found C, 59.20; H, 5.31; N, 5.90. DSC = 132.64 - 140.52°C at 50.30 J/g.

## Example 15

## Preparation of

1,1-dimethylethyl cis-4-[[[(3,4-dichlorophenyl)amino]carbonyl]amino]-5-oxo-1-(phenylmethyl)-3-pyrrolidinecarboxylate

To a solution of 3,4-dichlorophenyl isocyanate (194 mg, 1.0 mmol) in  $\text{CH}_2\text{Cl}_2$  (3 ml) was added aminopyrrolidinone of Example X (300 mg, 1.0 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 ml). After stirring for 48 h the solvent was concentrated in vacuo to give a solid which was chromatographed on silica gel eluting with 5% EtOH/ $\text{CH}_2\text{Cl}_2$  to give 425 mg (89%) of the title compound.

Anal Calcd for  $\text{C}_{23}\text{H}_{23}\text{N}_3\text{O}_4\text{Cl}_2$ : C, 57.75; H, 5.27; N, 8.78; Cl, 14.82. Found C, 57.93; H, 5.38; N, 8.65; Cl, 14.97. DSC = 188.62°C - 190.68°C at 78.73 J/g.

MS calcd for  $\text{C}_{23}\text{H}_{23}\text{N}_3\text{O}_4\text{Cl}_2$ , 478, found 478.

## Example 16

## Preparation of

Ethyl cis-4-[(2-naphthalenylcarbonyl)amino]-5-oxo-1-pentyl-3-pyrrolidinecarboxylate

To a solution of the aminopyrrolidinone of Example R (120 mg, 0.495 mmol) and triethylamine (0.35 ml, 2.48 mmol) in  $\text{CH}_2\text{Cl}_2$  was added a solution of 2-naphthoyl chloride (94 mg, 0.495 mmol) in  $\text{CH}_2\text{Cl}_2$  dropwise via syringe. After stirring for 12 h at room temperature the reaction mixture was evaporated in vacuo to give a residue which was chromatographed on silica gel eluting with  $\text{EtOH}/\text{CH}_2\text{Cl}_2$  (2%-5%) to give the title compound (172 mg, 69%) as a colorless solid. MS  $M+1$  calcd for  $\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}_4$  397; found 397.

## Example 17

## Preparation of

1,1-Dimethylethyl cis-4-[[ (2-naphthalenylamino)carbonyl]  
amino]-5-oxo-1-pentyl-3-pyrrolidinecarboxylate

To a solution of 2-naphthyl isocyanate (69 mg, 0.407 mmol) dissolved in 3 ml of  $\text{CH}_2\text{Cl}_2$  was added a solution of the amine of Example T (110 mg, 0.407 mmol) in 3 ml of  $\text{CH}_2\text{Cl}_2$  and the resulting solution was stirred for 16 h at room temperature. Evaporation of the solvent in vacuo gave a solid which was purified on silica gel eluting with 5/95 EtOH/ $\text{CH}_2\text{Cl}_2$  to give the title compound (130 mg, 73%) as a colorless solid. MS calcd for  $\text{C}_{25}\text{H}_{33}\text{N}_3\text{O}_4$  439, found 439.

## Example 18

## Preparation of

Ethyl cis-4-[(2-naphthalenylcarbonyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylate

To a solution of the aminopyrrolidinone of Example S (1.54 g, 6.2 mmol) and triethylamine (1.3 ml, 9.3 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 ml) was added a solution of 2-naphthoyl chloride (1.18 g, 6.2 mmol) in  $\text{CH}_2\text{Cl}_2$  (7 ml) dropwise via syringe. After stirring for 12 h at room temperature the reaction mixture was evaporated in vacuo to give a residue which was chromatographed on silica gel eluting with  $\text{EtOH}/\text{CH}_2\text{Cl}_2$  (2%-5%) to give the title compound (2.5 g, 100%) as a colorless solid. Anal calcd for  $\text{C}_{24}\text{H}_{22}\text{N}_2\text{O}_4$ : C, 71.63; H, 5.51; N, 6.96. Found C, 71.31; H, 5.45; N, 6.73. MS calcd for  $\text{C}_{24}\text{H}_{22}\text{N}_2\text{O}_4$ , 402; found 402.

## Example 19

## Preparation of

1,1-Dimethylethyl cis-4-[(2-naphthalenylcarbonyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylate

To a solution of 2-naphthoyl chloride (1.20 g, 6.29 mmol) in  $\text{CH}_2\text{Cl}_2$  (9 ml) was added a solution of aminopyrrolidinone of Example V (1.56 g, 5.64 mmol) and triethylamine (1.31 ml, 9.43 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 ml) and the resulting solution was stirred for 60 h at room temperature. After removing the solvent in vacuo,  $\text{H}_2\text{O}$  was added and the mixture was extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic layers were washed with brine, dried ( $\text{MgSO}_4$ ), filtered and concentrated under reduced pressure to give a solid which was chromatographed on silica gel eluting with 2% EtOH/ $\text{CH}_2\text{Cl}_2$  to give the title compound (2.28 g, 94%) as a colorless solid. Anal calcd for  $\text{C}_{26}\text{H}_{26}\text{N}_2\text{O}_4 \cdot 2/3\text{H}_2\text{O}$ : C, 70.57; H, 5.92; N, 6.33. Found: C, 70.36; H, 6.16; N, 6.23. MS calcd for  $\text{C}_{26}\text{H}_{26}\text{N}_2\text{O}_4$ , 430, found 430. DSC = 182.4-185.1°C at 107.4 J/g.

## Example 20

## Preparation of

1,1-Dimethylethyl cis-1-(2-fluorophenyl)-4-[(2-naphthalenylcarbonyl)amino]-5-oxo-3-pyrrolidinecarboxylate

To a solution of 2-naphthoyl chloride (178 mg, 0.934 mmol) in  $\text{CH}_2\text{Cl}_2$  (3 ml) was added a solution of aminopyrrolidinone of Example W (250 mg, 0.849 mmol) and triethylamine (146 mg, 1.44 mmol) in  $\text{CH}_2\text{Cl}_2$  (3 ml) and the resulting solution was stirred at room temperature for 18 h. The solvent was then removed in vacuo and the resulting foam was purified by radial chromatography on a silica gel plate (4 mm) eluting with 2/98 EtOH/ $\text{CH}_2\text{Cl}_2$  to give the title compound (380 mg, 100%) as a colorless foam. MS  $M+1$  calcd for  $\text{C}_{26}\text{H}_{25}\text{N}_2\text{O}_4\text{F}$  449, found 449. DSC = 142.2-151.5°C @ 55.9 J/g.



## Example 21

## Preparation of

1,1-dimethylethyl cis-4-[(2-naphthalenylcarbonyl)amino]-5-oxo-1-(phenylmethyl)-3-pyrrolidinecarboxylate

To a solution of 2-naphthoyl chloride (210 mg, 1.1 mmol) in  $\text{CH}_2\text{Cl}_2$  (3 ml) was added a solution of aminopyrrolidinone of Example X (300 mg, 1.0 mmol) and triethylamine (.24 ml, 1.7 mmol) in  $\text{CH}_2\text{Cl}_2$  (3 ml). After stirring for 18 h at room temperature the reaction mixture was evaporated in vacuo to give an oil which was purified by radial chromatography on silica gel eluting with  $\text{EtOH}/\text{CH}_2\text{Cl}_2$  (2%) to give the title compound 363 mg (82%).

DSC = 124.38 - 128.68°C @ 49.93 (99.73) J/g.

## Example 22

## Preparation of

1,1-Dimethylethyl cis-4-[[ (4-chlorophenyl) carbonyl] amino]-5-oxo-1-pentyl-3-pyrrolidinecarboxylate

To a solution of the aminopyrrolidinone of Example T (116 mg, 0.429 mmol) and triethylamine (0.12 ml, 0.858 mmol) in  $\text{CH}_2\text{Cl}_2$  was added a solution of 4-chlorobenzoyl chloride (75 mg, 0.429 mmol) in  $\text{CH}_2\text{Cl}_2$  dropwise via syringe. After stirring for 12 h at room temperature the reaction mixture was evaporated in vacuo to give a residue which was chromatographed on silica gel eluting with  $\text{EtOH}/\text{CH}_2\text{Cl}_2$  (2%-5%) to give the title compound (160 mg, 91%) as a colorless solid. DSC = 100.4-105.1°C at 52.7 J/g. Anal calcd for  $\text{C}_{21}\text{H}_{29}\text{N}_2\text{O}_4\text{Cl}$ : C, 61.68; H, 7.15; N, 6.85. Found C, 61.20; H, 7.06; N, 6.58. MS calcd for  $\text{C}_{21}\text{H}_{29}\text{N}_2\text{O}_4\text{Cl}$  409, found 409.

## Example 23

## Preparation of

Ethyl cis-4-[[ (4-chlorophenyl)carbonyl]amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylate

To a solution of p-chlorobenzoyl chloride (247 mg, 1.41 mmol) in  $\text{CH}_2\text{Cl}_2$  (4 ml) was added a solution of aminopyrrolidinone of Example S (350 mg, 1.41 mmol) and triethylamine (0.4 ml, 2.82 mmol) in  $\text{CH}_2\text{Cl}_2$  (4 ml) and the resulting solution was stirred for 18 h at room temperature. Concentration in vacuo gave an oil which was chromatographed on silica gel eluting with 5/95 EtOH/ $\text{CH}_2\text{Cl}_2$  to give the title compound (378 mg, 68%) as a solid. Anal calcd for  $\text{C}_{20}\text{H}_{19}\text{N}_2\text{O}_4\text{Cl}$ : C, 62.10; H, 4.95; N, 7.24. Found: C, 62.07; H, 5.05; N, 7.18. MS calcd for  $\text{C}_{20}\text{H}_{19}\text{N}_2\text{O}_4\text{Cl}$  386, found 386. DSC = 215.2-216.8°C at 144.3 J/g.

## Example 24

## Preparation of

ethyl cis-4-[[[(4-chlorophenyl)amino]carbonyl]amino]-5-oxo-1-pentyl-3-pyrrolidinecarboxylate

To a solution of 4-chlorophenyl isocyanate (113 mg, 0.734 mmol) in  $\text{CH}_2\text{Cl}_2$  (1 ml) was added the aminopyrrolidinone of Example R (178 mg, .734 mmol) in  $\text{CH}_2\text{Cl}_2$  (1 ml). After stirring for 18 h, the solvent was removed in vacuo and the resulting mixture was chromatographed on silica gel (5%  $\text{EtOH}/\text{CH}_2\text{Cl}_2$ ) to give the title compound (210 mg, 72%).

$^1\text{H}$  NMR (300  $\text{MHz}$ ,  $\text{CDCl}_3$ )  $\delta$  7.99 (1H, s), 7.42 (2H, d), 7.24 (2H, t), 6.21 (1H, d), 4.92 (1H, q), 4.21 (1H, m), 4.11 (1H, m), 3.55 (2H, q), 3.32 (2H, m), 1.55 (2H, q), 1.29 (4H, m), 1.21 (2H, t), 0.89 (3H, t).

## Example 25

## Preparation of

1,1-Dimethylethyl cis-4-[(1H-indazol-3-ylcarbonyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylate

To indazole-3-carboxylic acid (176 mg, 1.08 mmol) [prepared according to the procedure in J. Am Chem. Soc. 74, 2009 (1952)] in DMF (2 ml) was added 1,1-carbonyldiimidazole (176 mg, 1.08 mmol). After stirring for 4 h at room temperature a solution of the aminopyrrolidinone of Example V (300 mg, 1.08 mmol) in DMF was added. After stirring for 12 h at room temperature the reaction mixture was evaporated in vacuo to give 260 mg (57%) of an oil which was chromatographed on silica gel eluting with EtOH/CH<sub>2</sub>Cl<sub>2</sub> (2%-5%) to give the title compound.

Anal calcd for C<sub>23</sub>H<sub>24</sub>N<sub>4</sub>O<sub>4</sub>: C, 65.70; H, 5.75; N, 13.32. Found C, 65.73; H, 5.90; N, 13.12. DSC = 200.48°C - 205.71°C at 168.55 J/g.

## Example 26

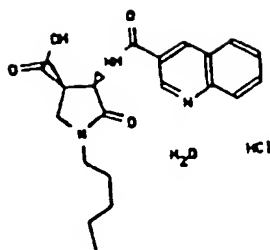
## Preparation of

1,1-Dimethylethyl cis-5-oxo-1-phenyl-4-[(2-pyrazinylcarbonyl) amino]-3-pyrrolidinecarboxylate

To 2-pyrazinecarboxylic acid (90 mg, 0.72 mmol) in DMF (2 ml) was added 1,1-carbonyldiimidazole (117 mg, 0.72 mmol). After stirring for 4 h at room temperature a solution of the aminopyrrolidinone of Example V (200 mg, 0.72 mmol) in DMF was added. After stirring for 18 h at room temperature the reaction mixture was evaporated in vacuo to give an oil which was chromatographed on silica gel eluting with EtOH/CH<sub>2</sub>Cl<sub>2</sub> (2%-5%) to give the title compound, 140 mg (51%). MS calcd for C<sub>20</sub>H<sub>22</sub>N<sub>4</sub>O<sub>4</sub>, 382, found 382.

## Example 27

## Preparation of



cis-5-oxo-1-pentyl-4-[(3-quinolinylcarbonyl)amino]-3-pyrrolidinecarboxylic acid, monohydrochloride

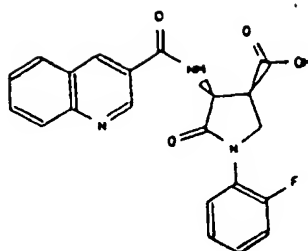
To the ethyl ester of Example 1 (173 mg, 0.435 mmol) dissolved in 4:1 EtOH/THF was added an aqueous solution of lithium hydroxide (31 mg, 1.29 mmol). After stirring for 16 h at room temperature 2.5 ml of water was added and the solution was extracted with chloroform. The aqueous layer was then acidified with 1N HCl to pH=2 and extracted again

with chloroform. The combined organic layers were dried over  $\text{MgO}_4$ , filtered and concentrated in vacuo to give the crude acid which was chromatographed on silica gel eluting with 5/95/1  $\text{EtOH}/\text{CH}_2\text{Cl}_2/\text{HOAc}$  to give the title compound (31 mg, 19%) as a colorless powder. MS  $\text{M}+1$  calcd for  $\text{C}_{20}\text{H}_{23}\text{N}_3\text{O}_4$  370; found 370.



## Example 28

## Preparation of



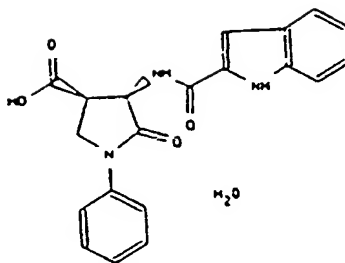
cis-1-(2-fluorophenyl)-5-oxo-4-[(3-quinolinylcarbonyl)amino]-  
5-oxo-3-pyrrolidinecarboxylic acid

The tert-butyl ester of Example 3 (223 mg, 0.496 mmol) was dissolved in trifluoroacetic acid (11 ml) and stirred for 8 h at room temperature. Concentration in vacuo gave a yellow oil which was purified by radial chromatography on a silica gel plate (2 mm) eluting with 10/89/1 EtOH/CH<sub>2</sub>Cl<sub>2</sub>/HOAc to give the title compound (178 mg, 63%). MS calcd for C<sub>21</sub>H<sub>16</sub>N<sub>3</sub>O<sub>4</sub>F 393, found 393. DSC = 293.2-297.4°C @ 147.7 J/g.

100

## Example 29

## Preparation of



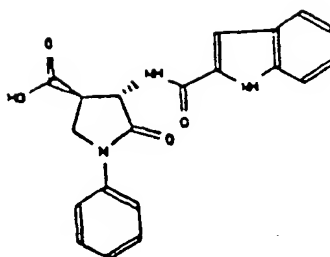
cis-4-[(1H-indol-2-ylcarbonyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid

The tert-butyl ester of Example 5 (110 mg, 0.26 mmol) was dissolved in 3 ml of trifluoroacetic acid and the resulting solution was stirred for 2 days at room temperature.

Concentration in vacuo gave an oil which was chromatographed on silica gel eluting with 5/91/1 EtOH/CH<sub>2</sub>Cl<sub>2</sub>/HOAc to give the title compound (41 mg, 43%) as a colorless solid. MS calcd for C<sub>20</sub>H<sub>17</sub>N<sub>3</sub>O<sub>4</sub>, 363, found 363. DSC = 214.2-229.3°C @ 48.7 J/g.

## Example 30

## Preparation of



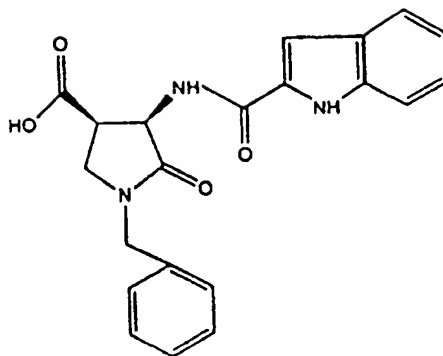
trans-4-[(1H-Indol-2-ylcarbonyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid

To the ethyl ester of Example 4 (68 mg, 0.174 mmol) dissolved in 4:1 EtOH/THF was added an aqueous solution of lithium hydroxide (13 mg, 0.521 mmol). After stirring for 16 h at room temperature, 2.5 ml of water was added and the solution was extracted with chloroform. The aqueous layer was then acidified with 1N HCl to pH2 and extracted again with chloroform. The combined organic layers were dried over

MgO<sub>4</sub>, filtered and concentrated in vacuo to give the crude acid which was chromatographed on silica gel eluting with 5/95/1 EtOH/CH<sub>2</sub>Cl<sub>2</sub>/HOAc to give the title compound (27 mg, 42%) as a colorless powder. Anal calcd for C<sub>20</sub>H<sub>17</sub>N<sub>3</sub>O<sub>4</sub>: C, 64.51; H, 4.87; N, 11.28. Found: C, 64.26; H, 4.62; N, 10.88. MS M+1 calcd for C<sub>20</sub>H<sub>17</sub>N<sub>3</sub>O<sub>4</sub> 364, found 364.

## Example 31

## Preparation of

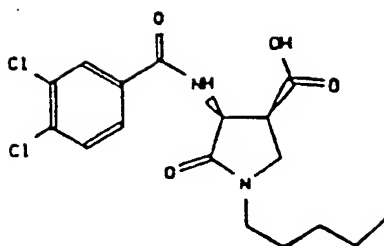


cis-4-[(1H-Indol-2-ylcarbonyl)amino]-5-oxo-1-(phenylmethyl)-3-pyrrolidinecarboxylic acid

The tert-butyl ester 320 mg (0.738 mmol) of Example 6 was dissolved in trifluoroacetic acid (2 ml) and stirred for 3.5 h at room temperature after which time the reaction was concentrated in vacuo. The resulting material was recrystallized from  $\text{CH}_2\text{Cl}_2$ , to give 94 mg (34%) of the title compound. Anal calcd for  $\text{C}_{21}\text{H}_{19}\text{N}_3\text{O}_4 \cdot \frac{1}{2}\text{H}_2\text{O}$ . C, 66.04; H, 5.15; N, 11.00. Found C, 66.21; H, 5.34; N, 10.62. MS calcd 377, found 377. DSC = 240.75-246.18°C @ 122.6 J/g.

## Example 32

## Preparation of



cis-4-[[ (3,4-Dichlorophenyl) carbonyl]amino]-5-oxo-1-pentyl-3-pyrrolidinecarboxylic acid

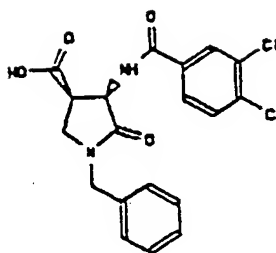
The tert-butyl ester of Example 9 (145 mg, 0.327 mmol) was dissolved in 5 ml of trifluoroacetic acid and stirred for 16 h at room temperature after which time the reaction was concentrated in vacuo. The resulting material was radially chromatographed on silica gel eluting with EtOH/CH<sub>2</sub>Cl<sub>2</sub>/HOAc (5/95/1) to give the title compound (89 mg, 77%) as a

colorless solid. Anal calcd for  $C_{17}H_{20}N_2O_4Cl_2$ : C, 52.73; H, 5.20; N, 7.23. Found: C, 52.43; H, 5.32; N, 7.02.

DSC = 204.6-210.2°C @ 54.8 J/g. MS M+1 calcd for  $C_{17}H_{20}N_2O_4Cl_2$  387, found 387.

## Example 33

## Preparation of



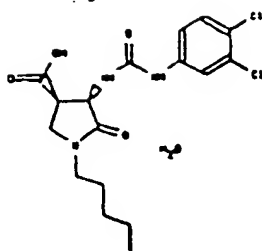
cis-4-[[[(3,4-dichlorophenyl)carbonyl]amino]-5-oxo-1-(phenylmethyl)-3-pyrrolidinecarboxylic acid

The tert-butyl ester of Example 14 (301 mg, 0.65 mmol) was dissolved in trifluoroacetic acid (3 ml) and stirred for 3.5 h after which time the reaction was concentrated in vacuo. The residue was resuspended in  $\text{CH}_2\text{Cl}_2$  and filtered to give 155 mg (58%) of the title compound as a solid. Anal Calcd for  $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}_4\text{Cl}_2 \cdot 1/4\text{H}_2\text{O}$ : C, 55.42; H, 4.04; N, 6.80. Found: C, 55.43; H, 4.13; N, 6.83. DSC = 217.26–219.87°C at 104.8 J/g. MS M+1 calcd for  $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}_4\text{Cl}_2$  408, found 408.



## Example 34

## Preparation of



cis-4-[[[(3,4-dichlorophenyl)amino]carbonyl]amino]-5-oxo-1-pentyl-3-pyrrolidinecarboxylic acid

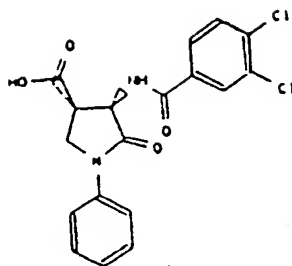
The tert-butyl ester of Example 10 (160 mg, 0.35 mmol) was dissolved in 5 ml of trifluoroacetic acid and stirred for 16 h at room temperature after which time the reaction was concentrated in vacuo. The resulting material was radially chromatographed on silica gel eluting with EtOH/CH<sub>2</sub>Cl<sub>2</sub>/HOAc (5/95/1) to give the title compound (119 mg, 85%) as a colorless solid. DSC = 139.0-143°C @ 5.7 J/g and 191.7-

203.5°C @ 99.6 J/g. MS M+1 calcd for  $C_{17}H_{21}N_3O_4Cl_2$  403, found  
403.

109

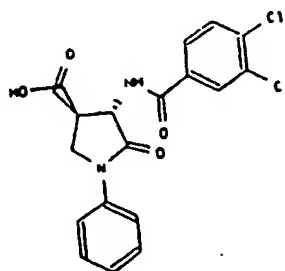
## Example 35

Preparation of



cis-4-[[[(3,4-dichlorophenyl)carbonyl]amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid (Compound A)

and



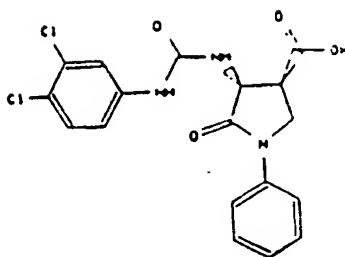
trans-4-[[ (3,4-dichlorophenyl) carbonyl] amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid (Compound B)

To a solution of ethyl ester of Example 11 (394 mg, 0.935 mmol) in EtOH/THF (10 ml, 4:1 EtOH/THF) was added a solution of lithium hydroxide (33 mg, 1.4 mmol) in 1 ml H<sub>2</sub>O and the resulting solution was stirred for 2 h at room temperature. Concentration in vacuo gave a solid which was chromatographed on silica gel eluting with 2/97/1 EtOH/CH<sub>2</sub>Cl<sub>2</sub>/HOAc to give the cis-substituted carboxylic acid Compound A (31 mg, 8.4%) as a colorless solid. Anal calcd for C<sub>18</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub>Cl<sub>2</sub>: C, 54.97; H, 3.59; N, 7.12. Found: C, 55.10; H, 3.61; N, 6.66. MS M+1 calcd for C<sub>18</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub>Cl<sub>2</sub> 394, found 394. DSC = 220-227.7°C at 70.9 J/g. Continued elution gave the trans-substituted carboxylic acid Compound B (290 mg, 79%) as a colorless solid. Anal calcd for C<sub>18</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub>Cl<sub>2</sub>: C, 54.97; H, 3.59; N, 7.12. Found: C, 54.70; H, 3.51; N, 6.98. MS M+1 calcd for C<sub>18</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub>Cl<sub>2</sub> 394, found 394. DSC = 234.2-237.0°C @ 80.1 J/g.

111

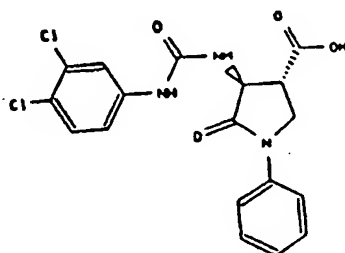
## Example 36

## Preparation of



cis-4-[[[(3,4-dichlorophenyl)amino]carbonyl]amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid (Compound A)

and

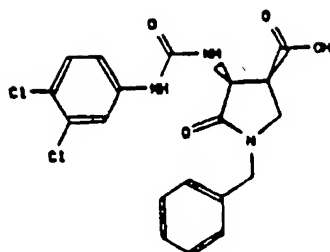


trans-4-[[[(3,4-dichlorophenyl)amino]carbonyl]amino-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid (Compound B)

To a solution of ethyl ester of Example 12 (420 mg, 0.96 mmol) in EtOH/THF (10 ml of 1:4 EtOH/THF) was added a solution of lithium hydroxide (35 mg, 1.4 mmol) in H<sub>2</sub>O (3 ml) and the resulting solution was stirred for 2 h at room temperature. The reaction mixture was then acidified to pH = 2 with 1 N HCl. Removal of the solvent gave a yellow solid which was chromatographed on silica gel eluting with 2/97/1 EtOH/CH<sub>2</sub>Cl<sub>2</sub>/HOAc to give the cis-substituted Compound A (62 mg, 16%) as a colorless solid. MS calcd for C<sub>18</sub>H<sub>15</sub>N<sub>3</sub>O<sub>4</sub>Cl<sub>2</sub>, 408, found 408. DSC = 229.1-238.7°C @ 281.6 J/g. Continued elution gave the trans-substituted Compound B (160 mg, 41%) as a colorless solid: MS calcd for C<sub>18</sub>H<sub>15</sub>N<sub>3</sub>O<sub>4</sub>Cl<sub>2</sub>, 408, found 408. DSC = 243.5-249.7°C @ 218.2 J/g.

## Example 37

## Preparation of

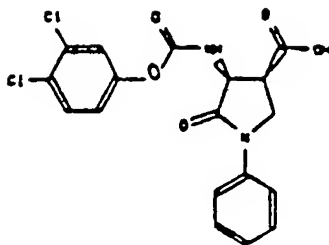


Cis-4-[[[(3,4-dichlorophenyl)amino]carbonyl]amino-5-oxo-1-phenylmethyl-3-pyrrolidinecarboxylic acid

The tert-butyl ester of Example 15 (410 mg, 0.857 mmol) was dissolved in trifluoroacetic acid (3 ml) and stirred for 4 h after which time the reaction was concentrated in vacuo. The residue was resuspended in MeOH and filtered to give the title compound (143 mg, 40%) as a solid. Anal calcd for  $C_{19}H_{17}N_3O_4Cl_2 \cdot 1/4H_2O$ : C, 53.47; H, 4.13; N, 9.85. Found C, 53.24; H, 4.12; N, 9.63. DSC = 213.82-216.88°C @ 121.3 J/g.

## Example 38

## Preparation of



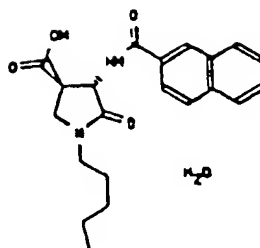
cis-4-[[ (3,4-Dichlorophenoxy) carbonyl]amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid

The tert-butyl ester of Example 13 is dissolved in trifluoroacetic acid and stirred for 16 h at room temperature after which time the reaction is concentrated in vacuo. The resulting material is purified by chromatography on silica gel eluting with EtOH/CH<sub>2</sub>Cl<sub>2</sub>/HOAc to give the title compound.



## Example 39

## Preparation of



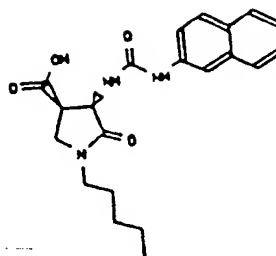
trans-4-[(2-Naphthalenylcarbonyl)amino]-5-oxo-1-pentyl-3-pyrrolidinecarboxylic acid

To the ethyl ester of Example 16 (170 mg, 0.429 mmol) dissolved in 4:1 EtOH/THF was added an aqueous solution of lithium hydroxide (31 mg, 1.29 mmol). After stirring for 16 h at room temperature, 2.5 ml of water was added and the solution was extracted with chloroform. The aqueous layer was then acidified with 1N HCl to pH=2 and extracted again with chloroform. The combined organic layers were dried over MgO<sub>4</sub>, filtered and concentrated in vacuo to give the crude

acid which was chromatographed on silica gel eluting with 5/95/1 EtOH/CH<sub>2</sub>Cl<sub>2</sub>/HOAc to give the title compound (45 mg, 28%) as a colorless powder. Anal calcd for C<sub>21</sub>H<sub>26</sub>N<sub>2</sub>O<sub>3</sub>·H<sub>2</sub>O: C, 65.27; H, 6.26; N, 7.61. Found C, 65.45; H, 6.52; N, 7.11. MS M+1 calcd for C<sub>21</sub>H<sub>26</sub>N<sub>2</sub>O<sub>3</sub>, 369, found 369.

## Example 40

## Preparation of



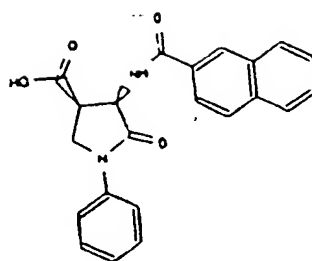
cis-4-[[[2-Naphthalenylamino)carbonyl]amino]-5-oxo-1-pentyl-3-pyrrolidinecarboxylic acid

The tert-butyl ester of Example 17 (130 mg, 0.296 mmol) was dissolved in 5 ml of trifluoroacetic acid and stirred for 16 h at room temperature after which time the reaction was concentrated in vacuo. The resulting material was chromatographed on silica gel on a chromatotron plate eluting with EtOH/CH<sub>2</sub>Cl<sub>2</sub>/HOAc (5/95/1) to give the title compound (63 mg, 55%) as a colorless solid. Anal calcd. for C<sub>21</sub>H<sub>25</sub>N<sub>3</sub>O<sub>3</sub>: C,

65.78; H, 6.57; N, 10.96. Found: C, 65.31; H, 6.62; N, 10.75. DSC = 228.8-231.3 at 293.2 J/g. MS calcd for  $C_{21}H_{25}N_3O_5$ , 383, found 383.

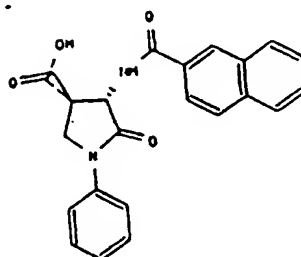
## Example 41

Preparation of



cis-4-[(2-Naphthalenylcarbonyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid (Compound A)

and



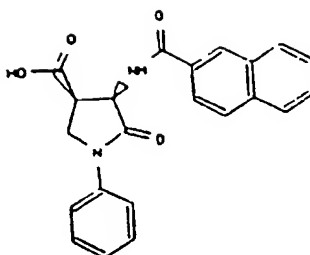
trans-4-[(2-Naphthalenylcarbonyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid (Compound B)

To the ethyl ester of Example 18 (1.92 g, 4.8 mmol) dissolved in 4:1 EtOH/THF (100 ml) was added a solution of lithium hydroxide (575 mg, 24 mmol). After stirring for 2 h at room temperature, 70 ml of water was added and the solution was extracted with chloroform. The aqueous layer was then acidified with 1N HCl to pH=2 and extracted again with chloroform. The combined organic layers were dried over  $MgO_4$ , filtered and concentrated in vacuo to give the crude acid which was recrystallized from  $CH_2Cl_2$  to give the trans carboxylic acid Compound B (1.19 g, 66%) as a colorless powder. Anal calcd for  $C_{22}H_{18}N_2O_4 \cdot 1/2H_2O$ : C, 68.92; H, 4.99; N, 7.30. Found: C, 68.57; H, 4.68; N, 7.17. MS M+1 calcd for  $C_{22}H_{18}N_2O_4$  375; found 375. DSC = 250.0-251.9 at 112.3 J/g. Chromatography of the mother liquor on silica gel eluting with 10/89/1 EtOH/ $CH_2Cl_2$ /HOAc gave the higher-Rf, cis isomer Compound A (232 mg, 12%) as a colorless powder. Anal calcd for  $C_{22}H_{18}N_2O_4 \cdot 1/4H_2O$ : C, 69.74; H, 4.92; N, 7.39. Found: C, 69.90; H, 4.94; N, 7.19. DSC = 211.7-214.9°C at 94.5 J/g. MS calcd for  $C_{22}H_{18}N_2O_4$  374, found 374.

121

## Example 42

## Preparation of



cis-4-[(2-Naphthalenylcarbonyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid

The tert-butyl ester of Example 19 (2.14 g, 7.97 mmol) was dissolved in 10 ml of trifluoroacetic acid and stirred for 18 h at room temperature after which time the reaction was concentrated in vacuo. The resulting solid was purified by chromatography on silica gel eluting with MeOH/CH<sub>2</sub>Cl<sub>2</sub>/HOAc (3/96/1) to give the title compound (1.56 g, 84%) as a colorless solid. Anal calcd for C<sub>22</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>·1/4H<sub>2</sub>O: C, 69.74; H,

122

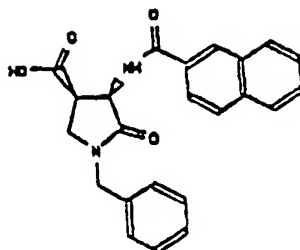
4.92; N, 7.39. Found: C, 69.90; H, 4.86; N, 7.30. MS calcd  
for  $C_{22}H_{18}N_2O_4$ , 374, found 374. DSC = 212.9-216.0°C at 100.9  
J/g.



123

## Example 43

## Preparation of

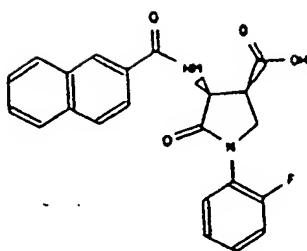


cis-4-[(2-Naphthalenylcarbonyl)amino]-5-oxo-1-(phenylmethyl)-3-pyrrolidinecarboxylic acid

The tert-butyl ester of example 21 (303 mg, 0.7 mmol) was dissolved in trifluoroacetic acid (3 ml) and stirred for 3.5 h after which time the reaction was concentrated in vacuo. Resuspension of the residue in  $\text{CH}_2\text{Cl}_2$  and filtration gave the title compound (161 mg, 59%) as a solid. Anal calcd for  $\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}_4 \cdot 1/4\text{H}_2\text{O}$ : C, 70.30; H, 5.26; N, 7.13. Found C, 70.52; H, 5.44; N, 7.10. DSC = 213.37–216.45°C @ 107.5 J/g. MS calc for  $\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}_4$  388, found 388.

## Example 44

## Preparation of



cis-1-(2-Fluorophenyl)-4-[(2-naphthalenylcarbonyl)amino]-5-oxo-3-pyrrolidinecarboxylic acid

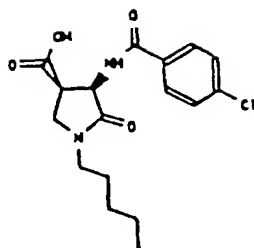
The tert-butyl ester of Example 20 (388 mg, 0.865 mmol) was dissolved in 3 ml of trifluoroacetic acid and stirred for 18 h at room temperature. Concentration in vacuo gave a solid which was chromatographed on a silica gel chromatotron plate (4 mm) eluting with 3/1/96 EtOH/CH<sub>2</sub>Cl<sub>2</sub>/HOAc to give the title compound (183 mg, 54%) as a solid. Anal calcd for C<sub>22</sub>H<sub>17</sub>N<sub>2</sub>O<sub>4</sub>F. H<sub>2</sub>O: C, 66.40; H, 4.67; N, 6.83. Found: C, 64.55; H, 4.42;

125

N, 6.71. MS calcd for  $C_{22}H_{17}N_2O_4F$  392, found 392. DSC = 182.9-185.2°C @ 94.1 J/g.

## Example 45

## Preparation of



cis-4-[[[(4-Chlorophenyl)carbonyl]amino]-5-oxo-1-pentyl-3-pyrrolidinecarboxylic acid

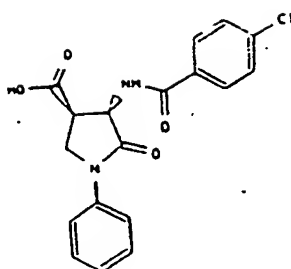
The tert-butyl ester of Example 22 (160 mg, 0.39 mmol) was dissolved in 4 ml of trifluoroacetic acid and stirred for 16 h at room temperature after which time the reaction was concentrated in vacuo. The resulting material was chromatographed on silica gel on a chromatotron plate eluting with EtOH/CH<sub>2</sub>Cl<sub>2</sub>/HOAc (5/95/1) to give the title compound (65

mg, 41%) as a colorless solid. DSC = 193.3-195.8°C @ 71.2 J/g.

MS calcd for  $C_{17}H_{21}N_2O_4Cl$  352, found 352.

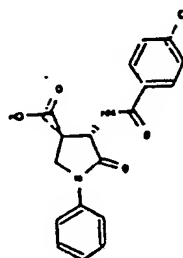
## Example 46

Preparation of



cis-4-[[4-Chlorophenyl]carbonylamino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid (Compound A)

and



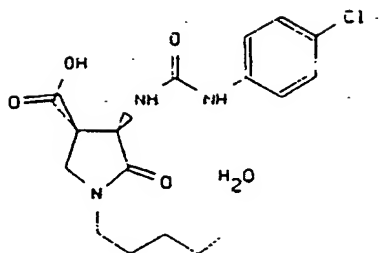
trans-4-[[ (4-Chlorophenyl)carbonyl]amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid (Compound B)

To a solution of ethyl ester of Example 23 (378 mg, 0.977 mmol) in EtOH/THF (10 ml of 1:4 EtOH THF) was added a solution of lithium hydroxide (35 mg, 0.147 mmol) in H<sub>2</sub>O (1 ml) and the resulting solution was stirred for 2 h at room temperature. Concentration in vacuo gave a residue which was chromatographed on silica gel eluting with 2/97/1 EtOH/CH<sub>2</sub>Cl<sub>2</sub>/HOAc to give the desired cis-substituted Compound A (28 mg, 8%) as a colorless solid. MS M+1 calcd for C<sub>18</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub>Cl 359, found 359. DSC = 211.71-220.08 @ 51.42 J/g. Continued elution afforded the trans-substituted carboxylic acid Compound B (213 mg, 61%) as a colorless solid. Anal calcd for C<sub>18</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub>Cl.1/2H<sub>2</sub>O: C, 58.79; H, 4.38; N, 7.61. Found: C, 58.41; H, 4.35; N, 7.10. MS calcd for C<sub>18</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub>Cl 358, found 358. DSC = 216.2-223.0°C @ 84.2 J/g.

130

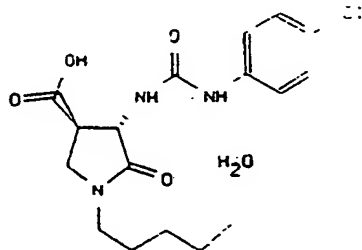
## Example 47

Preparation of



cis-4-[[[(4-chlorophenyl)amino]carbonyl]amino]-5-oxo-1-pentyl-3-pyrrolidinecarboxylic acid

and



trans-4-[[[(4-chlorophenyl)amino]carbonyl]amino]-5-oxo-1-pentyl-3-pyrrolidinecarboxylic acid

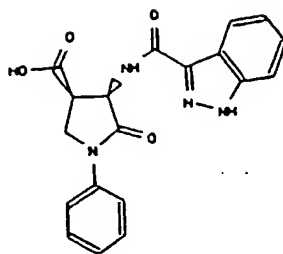


To a solution of the ethyl ester (210 mg, 0.530 mmol) of example 24 in 1:4 EtOH/THF (4 ml) was added a solution of lithium hydroxide (13 mg, 0.53 mmol) in water (1 ml) and the reaction was stirred at room temperature for 2 h. The reaction mixture was acidified with 1N HCl to pH=4 and concentrated in vacuo to give a solid which was purified by chromatography on silica gel eluting with MeOH/CH<sub>2</sub>Cl<sub>2</sub>/HOAc (10/89/1) to give the cis isomer (70. mg, 38%): Anal calcd for C<sub>17</sub>H<sub>22</sub>N<sub>3</sub>O<sub>4</sub>Cl.H<sub>2</sub>O: C, 52.92; H, 5.75; N, 10.89. Found: C, 52.97; H, 5.64; N, 10.36. MS calcd for C<sub>17</sub>H<sub>22</sub>N<sub>3</sub>O<sub>4</sub>Cl 368, found 368. Continued elution gave the trans isomer (88 mg, 45%).

Anal calcd for C<sub>17</sub>H<sub>22</sub>N<sub>3</sub>O<sub>4</sub>Cl:H<sub>2</sub>O: C, 52.92; H, 5.75; N, 10.89. Found: 53.17; H, 5.79; N, 10.40. MS calcd for C<sub>17</sub>H<sub>22</sub>N<sub>3</sub>O<sub>4</sub>Cl 368, found 368.

## Example 48

## Preparation of



cis-4-[(1H-Indol-3-ylcarbonyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid

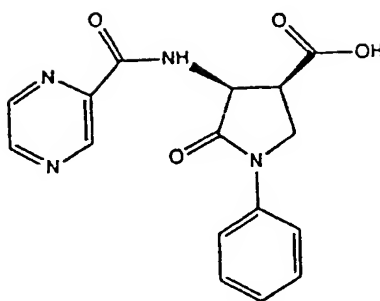
The tert-butyl ester (230 mg 0.547 mmol) of Example 25 was dissolved in trifluoroacetic acid (3 ml) and stirred for 20 min at room temperature after which time the reaction was concentrated in vacuo. Resuspension of the residue in  $\text{CH}_2\text{Cl}_2$  and filtration gave the title compound (206 mg, 79%) as a colorless solid. Anal calcd for  $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}_4 \cdot 8/10\text{CF}_3\text{CO}_2\text{H}$ :

133

C, 54.41; H, 3.55; N, 12.32; F, 10.03. Found C, 54.52; H, 3.76;  
N, 12.45; F, 10.35. DSC = 130.85-140.96°C at 97.64 J/g. MS  
calc. for  $C_{19}H_{16}N_4O_4$  364, found 364.

## Example 49

## Preparation of

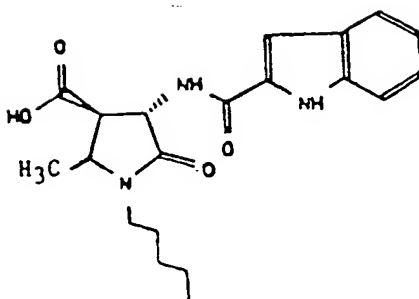


cis-5-Oxo-1-phenyl-4-[(2-pyrazinylcarbonyl)amino]-3-pyrrolidinecarboxylic acid

The tert-butyl ester (120 mg 0.314 mmol) of Example 26 was dissolved in trifluoroacetic acid 2 ml and stirred for 3.5 h at room temperature after which time the reaction was concentrated in vacuo. The resulting material was chromatographed on silica gel eluting with EtOH/CH<sub>2</sub>Cl<sub>2</sub>/HOAc (5/95/1) to give 55 mg (54%) of the title compound, MS calcd for C<sub>16</sub>H<sub>14</sub>N<sub>4</sub>O<sub>4</sub>: 326, found 326.

## Example 50

## Preparation of

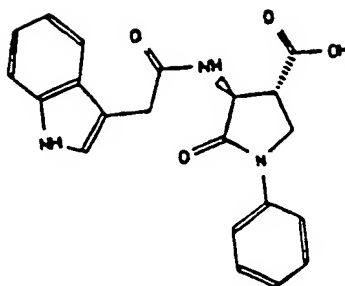


4-[(1H-Indol-2-ylcarbonyl)amino]-2-methyl-5-oxo-1-pentyl-3-pyrrolidinecarboxylic acid

To a solution of Example 7 (600 mg, 1.5 mmol) in EtOH/THF (20 ml of 1:4 EtOH/THF) was added a solution of lithium hydroxide (55 mg, 2.3 mmol) in H<sub>2</sub>O (10 ml) and the resulting solution was stirred for 2 h at room temperature. The reaction mixture was then acidified to pH 2 with 1N HCl. Removal of the solvent gave the title compound.

## Example 51

## Preparation of



trans-4-[(3-indolylacetyl)amino]-5-oxo-1-phenyl-3-  
pyrrolidinecarboxylic acid

To the title compound of example 8 (520 mg, 1.28 mmol) in 1:4 THF/EtOH (20 ml) was added lithium hydroxide (46 mg (1.92 mmol) in H<sub>2</sub>O (10 ml) and stirred for 2.5 h. The reaction mixture was acidified with 1N HCl to pH 3 and concentrated in vacuo. The mixture was purified by chromatography on silica gel (CH<sub>3</sub>OH/HOAc/CH<sub>2</sub>Cl<sub>2</sub> gradient 10/1/89 to 20/1/79) to give 124 mg (18%) of the title compound. MS calcd for C<sub>21</sub>H<sub>19</sub>N<sub>3</sub>O<sub>4</sub>: 377, found 377.

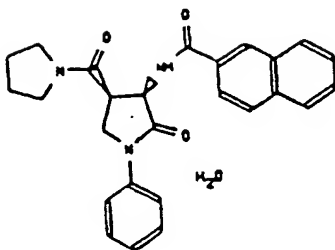
**Example 52****Preparation of**

**cis-4-[(2-Naphthalenylcarbonyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxamide**

The product of example 42 is treated with oxalyl chloride and a catalytic amount of DMF in  $\text{CHCl}_3$ . After 2 h at room temperature the solution is concentrated in vacuo. The acid chloride is then redissolved in  $\text{CHCl}_3$  and treated with gaseous ammonia. An aqueous workup and purification via chromatography affords the title compound.

## Example 53

## Preparation of



cis-1-[[3-[(2-Naphthalenylcarbonyl)amino]-2-oxo-1-phenyl-4-pyrrolidinyl]carbonyl]pyrrolidine

To the product of Example 42 (100 mg, 0.264 mmol) in DMF (2.5 ml) was added 1,1-carboxyldiimidazole (43 mg, 0.264 mmol). After stirring for 3 h at room temperature, pyrrolidinone (19 mg, 0.264 mmol) was added and the reaction was then stirred for 18 h at room temperature. After removal of the solvent in vacuo, a solution of  $K_2CO_3$  (36 mg) in  $H_2O$  (5 ml) was added and the mixture was extracted with  $CH_2Cl_2$ . The  $CH_2Cl_2$  extractions were washed with  $H_2O$  and brine and then dried

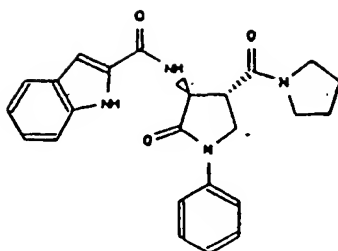


(MgO<sub>4</sub>) and concentrated to give an oil which was chromatographed on a silica gel chromatotron plate (2 mm) eluting with 5% EtOH/CH<sub>2</sub>Cl<sub>2</sub> to give the diamide title compound (32 mg, 28%). Anal calcd for C<sub>26</sub>H<sub>24</sub>N<sub>3</sub>O<sub>3</sub>·H<sub>2</sub>O: C, 70.10; H, 6.11; N, 9.43. Found: C, 70.27; H, 5.77; N, 9.24. MS calcd for C<sub>26</sub>H<sub>24</sub>N<sub>3</sub>O<sub>3</sub>, 427, found 427. DSC = 208.6-209.8°C @ 96 J/g.

140

## Example 54

## Preparation of

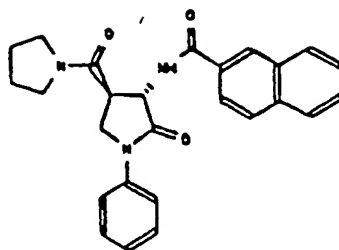


trans-N-[2-oxo-1-phenyl-4-(1-pyrrolidinylcarbonyl)-3-pyrrolidinyl]-1H-indole-2-carboxamide

To a solution of the product of example 30 (103 mg, 0.283 mmol) in DMF (2 ml) was added 1,1-carbonyldiimidazole (46 mg, 0.283 mmol). After stirring for 5.5 h, pyrrolidine (.05 ml, .566 mmol) was added and the reaction was stirred for 18 h. The resulting precipitate was filtered and then worked with CH<sub>3</sub>OH to give 91 mg (77%) of the title compound. MS calcd for C<sub>24</sub>H<sub>24</sub>N<sub>4</sub>O<sub>3</sub>: 416, found 416. DSC=218.72-234.43°C.

## Example 55

## Preparation of



trans-1-[[3-[(2-Naphthalenylcarbonyl)amino]-2-oxo-1-phenyl-4-pyrrolidinyl]carbonyl]pyrrolidine

To a solution of the product of Example 41 (Compound B) (106 mg, 0.28 mmol) in DMF (2 ml) was added 1,1-carbonyldiimidazole (45 mg, 0.28 mmol). After stirring for 5 h, pyrrolidine (0.23 ml, 2.8 mmol) was added and the reaction was stirred for 48 h at room temperature. Evaporation of the solvent in vacuo gave a yellow oil which was purified by radial chromatography (silica gel, 2 mm plate) eluting with 3% EtOH/CH<sub>2</sub>Cl<sub>2</sub> to give the title diamide compound (80 mg, 67%). Anal calcd for C<sub>26</sub>H<sub>24</sub>N<sub>3</sub>O<sub>3</sub>·1/2H<sub>2</sub>O: C, 71.54; H, 6.00; N,

142

9.62. Found: C, 71.38; H, 6.08; N, 9.31. MS calcd for  $C_{26}H_{24}N_3O_3$ , 427, found 427. DSC = 206.8-208.1°C @ 79.9 J/g.

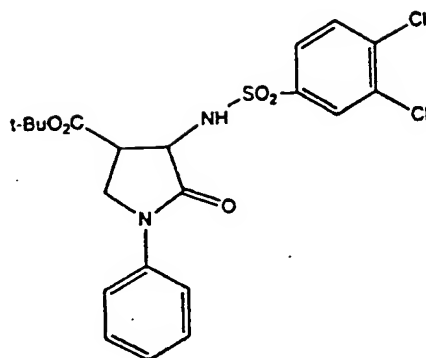
## Example 56

Preparation of  
trans-4-[(2-Naphthalenylcarbonyl)amino]-5-oxo-1-phenyl-3-  
pyrrolidine carboxamide

The trans-product of example 41 is converted to the  
corresponding primary amide via the acid chloride as  
described for example 52.

## Example 57

## Preparation of



1,1-Dimethylethyl cis-4-[[[(3,4-dichlorophenyl)sulfonyl]amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid

To a solution of the aminopyrrolidinone (150 mg, 5.43 mmol) of Example V and triethylamine (.15 ml, 10.9 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 ml) was added 3,4-dichlorophenylsulfonyl chloride (133 mg 5.43 mmol). The reaction was then stirred for 18 h at room temperature after which time the solvent was evaporated. The residue was chromatographed on silica gel eluting with  $\text{EtOH}/\text{CH}_2\text{H}_2$  (3/97) to give the desired title sulfonamide, 180 mg (73%). Anal. calcd. for  $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_3\text{Cl}_2\text{S}$ : C, 51.97; H, 4.57;

145

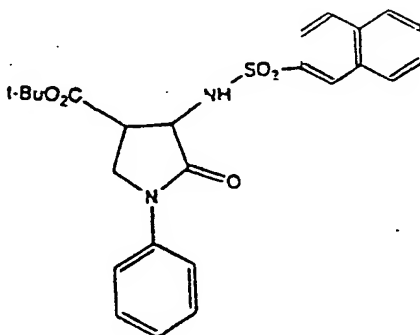
N, 5.77. Found C, 51.50; H, 4.61; N, 5.58. MS calcd. for:

$C_{21}H_{22}N_2O_3Cl_2S$  585, Found 484.

## Example 58

## Preparation of

1,1-dimethylethyl cis-4-[(2-naphthalenylsulfonyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylate



To a solution of 2-naphthalene sulfonylchloride (0.238 mg, 1.05 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 ml) was added a solution of the aminopyrrolidinone of Example V (0.290 mg, 1.05 mmol) and

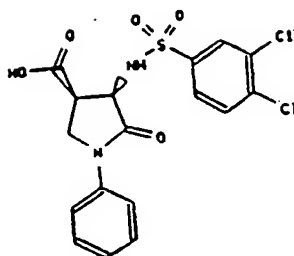


triethylamine (0.15 ml, 1.05 mmol) in  $\text{CH}_2\text{Cl}_2$  (3 ml) and stirred for 18 h. The desired solid was then filtered. The filtrate was purified by radial chromatography (2% EtOH/ $\text{CH}_2\text{H}_2$ ) to give additional desired material. Recrystallization of the combined solids from  $\text{CH}_2\text{Cl}_2$  afforded the title compound (375 mg, 80%). Anal. calcd. for  $\text{C}_{25}\text{H}_{26}\text{N}_2\text{O}_5\text{S} \cdot 1/3\text{H}_2\text{O}$ : C, 63.54; H, 5.69; N, 5.93. Found: C, 63.86; H, 5.69; N, 5.71. DSC = 192.01 - 194.52°C at 73.88 J/g.

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## Example 59

## Preparation of



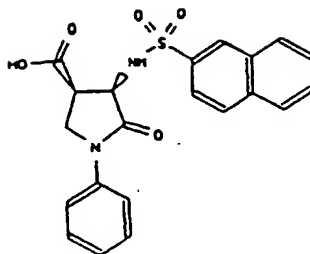
cis-4-[[3,4-Dichlorophenyl)sulfonyl]amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid

The title compound of Example 57 (140 mg, 0.288 mmol) was dissolved in trifluoroacetic acid (2 ml) and stirred for 3.5 h at room temperature after which time the reaction was concentrated in vacuo. Resuspension of the residue in  $\text{CH}_2\text{Cl}_2$  and filtration gave 84 mg (68%) of the title compound as a solid. Anal. calcd. for  $\text{C}_{17}\text{H}_{14}\text{N}_2\text{SO}_5\text{Cl}_2$ : C, 47.57; H, 3.29; N, 6.53. Found: C, 47.26; H, 3.25; N, 6.49. MS calcd. for

$C_{17}H_{14}N_2SO_3Cl_2$  430, found 430. DSC = 168.46°C at 32.01 J/g and  
174.86°C at 30.17 J/g.

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## Example 60



cis-4-[(2-Naphthalenylsulfonyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid

The tert-butyl ester of example 58 (320 mg, .686 mmol) was dissolved trifluoroacetic acid (2 ml) and stirred for 2.5 h after which time the reaction was concentrated in vacuo. The resulting material was recrystallized from  $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$  to give 116 mg (41%) of the title compound as a white solid. Anal. calcd. for  $\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}_5\text{S} \cdot 1/4\text{H}_2\text{O}$ : C, 60.79; H, 4.49; N, 6.75. Found: C, 60.94; H, 4.45; N, 6.71. MS calc for  $\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}_5\text{S}$  410, found 410. DSC = 221.0 - 224.1°C at 109.2 J/g.

## Example 61

Preparation of  
1-Phenyl-2,3-pyrrolidinedione

According to the procedure of Southwick [J. Org. Chem. 21, 1087 (1956)] the ethyl ester pyrrolidinone of Example S (1.0 g, 4.0 mmol) was suspended in 75 ml of 20% HCl/H<sub>2</sub>O and refluxed for 3.5 h. The reaction was cooled and filtered and the filtrate was extracted with CHCl<sub>3</sub> (4 X 150 ml).

Concentration of the combined extracts gave an off-white solid (358 mg). <sup>1</sup>NMR(300 MHz, CDCl<sub>3</sub>) δ 2.92 (t, 2H), 4.17 (t, 2H), 7.32 (t, 1H), 7.98 (t, 2H), 7.84 (d, 2H).

## Example 62

## Preparation of

## Ethyl 4,5-dioxo-1-phenyl-3-pyrrolidineacetate

A solution of the product of Example 61 in THF is added to a solution of lithium di-iso-propylamide (LDA) in THF at  $-78^{\circ}\text{C}$ . After 2 h at  $-78^{\circ}\text{C}$  a solution of ethyl bromoacetate is added and the reaction is allowed to warm to room temperature. After an aqueous workup the crude product is chromatographed on silica gel to give the title compound.

## Example 63

## Preparation of

## Ethyl 4-(hydroxyimino)-5-oxo-1-phenyl-3-pyrrolidineacetate

A solution of product of Example 62 in pyridine is treated with an excess of hydroxylamine hydrochloride and the reaction is stirred at room temperature for 2 d. The solution is concentrated in vacuo and the residue is chromatographed on silica gel to give the title compound.

## Example 64

## Preparation of

## Ethyl 4-amino-5-oxo-1-phenyl-3-pyrrolidineacetate

A solution of the product of example 63 in EtOH is hydrogenated with 10% palladium on carbon at 60 psi at 60°C. Filtration and purification of the product on silica gel affords the title compound.



## Example 65

Preparation of

cis-4-[(1H-Indol-2-ylcarbonyl)amino]-5-oxo-1-phenyl-3-pyrrolidineacetic acid

The aminopyrrolidinone of Example 63 is coupled with indole-2-carboxylic acid according to the procedure described in Example 4 and the resulting ester is saponified to give the title homologated acid.

## Example 66

## Preparation of

3-[[2-(Methoxymethyl)-1-pyrrolidinyl]imino]-1-phenyl-2-pyrrolidinone

A solution of the product of Example 61 and chiral 1-amino-2-methoxymethylpyrrolidine (SAMP or RAMP; 1 equiv) in benzene is refluxed under Dean-Stark conditions for 20 h. After cooling, Et<sub>2</sub>O is added and the mixture is washed with water. The organic layer is dried (MgO<sub>4</sub>) and evaporated to give a residue which is chromatographed on silica gel to give the title compound.

## Example 67

## Preparation of

Ethyl 4-[[2-(methoxymethyl)-1-pyrrolidinyl]imino]-1-phenyl-5-oxo-3-pyrrolidineacetate

To a solution of SAMP hydrazone of Example 66 or RAMP hydrazone of Example 66 in anhydrous THF at  $-78^{\circ}\text{C}$  is added dropwise a solution of tert-butyllithium (1.1 equiv) in n-hexane and the mixture is stirred for 2 h at  $-78^{\circ}\text{C}$ . The solution of metalated hydrazone is cooled to  $-100^{\circ}\text{C}$  and a solution of ethyl bromoacetate (1.2 equiv) in anhydrous THF is added dropwise and the mixture is stirred for 1 h at  $-100^{\circ}\text{C}$  and then warmed slowly to room temperature over 15 h. Finally,  $\text{Et}_2\text{O}$  is added and the mixture is washed with pH7-buffer and brine, dried ( $\text{MgO}_4$ ) and evaporated under reduced pressure to give a residue which is chromatographed on silica gel eluting with  $\text{EtOH}/\text{CH}_2\text{Cl}_2$  to give the title alkylated hydrazone in high diastereomeric excess.

## Example 68

Preparation of enantiomerically pure

Ethyl cis-4-amino-5-oxo-1-phenyl-3-pyrrolidineacetate

A solution of SAMP hydrazone of Example 67 or the RAMP hydrazone of Example 67 in EtOH is hydrogenated with 10% palladium on carbon at 1200 psi at 70°C for 24 h. Filtration and evaporation of the filtrate gives a residue which is chromatographed on silica gel eluting with 2% EtOH/CH<sub>2</sub>Cl<sub>2</sub> to give the desired title compound. Alternatively the hydrazone of Example 67 in anhydrous THF is treated with catecholborane followed by treatment with Raney Nickel. Filtration and evaporation of the filtrate gives a residue which is chromatographed on silica gel to give the title compound.

## Example 69

Preparation of enantiomerically pure

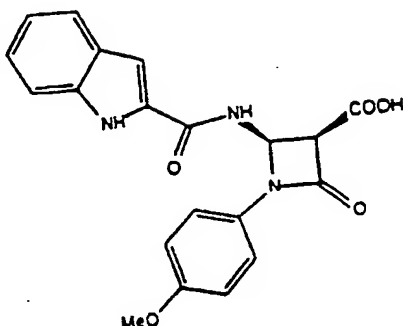
cis-4-[(1H-Indol-2-ylcarbonyl)amino]-5-oxo-1-phenyl-3-pyrrolidineacetic acid

To a solution of indole-2-carboxylic acid in DMF is added 1 equivalent of 1,1-carbonyldiimidazole. After stirring for 4 h at room temperature a solution of the aminopyrrolidinone of Example 68 in DMF is added. After stirring for 12 h at room temperature the reaction mixture is evaporated in vacuo to give a residue which is chromatographed on silica gel to give the desired amide. To a solution of the amide in 1:4 EtOH/THF is added a solution of lithium hydroxide (1.4 equiv) in H<sub>2</sub>O and the resulting solution is stirred for 2 h at room temperature. The reaction mixture is then acidified to pH = 2 with 1 N HCl. Removal of the solvent gives a residue which is chromatographed on silica gel to give the title carboxylic acid as a single enantiomer.

## Example 70

Preparation of

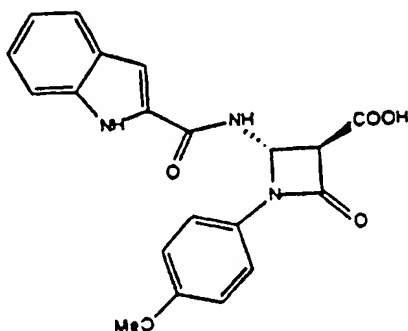
cis-N-(p-Methoxyphenyl)-3-carboxy-4-(1H-indol-2'-ylcarbonyl)  
aminoazetidin-2-one



Cis-N-(p-methoxyphenyl)-3-carboxy-4-dibenzylaminoazetidin-2-one t-butyl ester (T. Hiyama et al., J. Amer. Chem. Soc. (1989), 111, 6843) is hydrogenolyzed with 10% Pd-C/ammonium formate to afford cis-N-(p-methoxyphenyl)-3-carboxy-4-aminoazetidin-2-one t-butyl ester, which is not isolated but reacted directly with indole-2-carboxylic acid-carbonyldiimidazole/THF to give cis-N-(p-methoxyphenyl)-3-carboxy-4-(1H-indol-2'-yl)aminoazetidin-2-one t-butyl ester. Removal of the t-butyl ester with trifluoroacetic acid affords the title compound.

## Example 71

Preparation of  
trans-N-(p-Methoxyphenyl)-3-carboxy-4-(1H-indol-2'-yl  
carbonyl)aminoazetidin-2-one

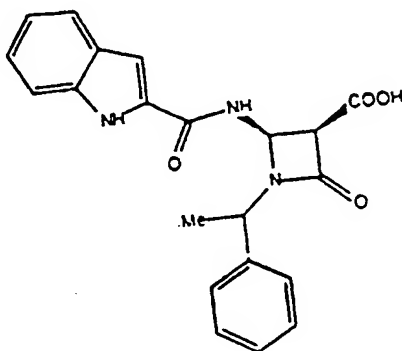


Following the procedure of Example 70, trans-N-(p-methoxyphenyl)-3-carboxy-4-dibenzylaminoazetidin-2-one t-butyl ester (T. Hiyama et al., J. Amer. Chem. Soc. (1989), 111, 6843) is converted to the title compound.

## Example 72

Preparation of

cis-N-(1'-Phenylethyl)-3-carboxy-4-(1H-indol-2"-ylcarbonyl)aminoazetidin-2-one

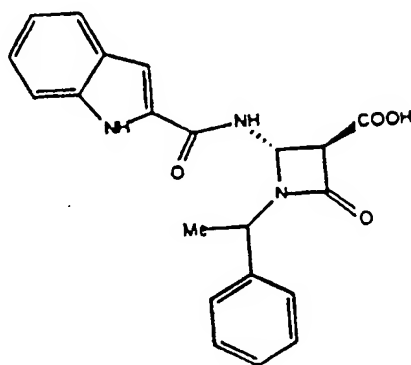


Following the procedure of Example 70, cis-N-(1'-phenylethyl)-3-carboxy-4-dibenzylaminoazetidin-2-one t-butyl ester (T. Hiyama et al., J. Amer. Chem. Soc. (1989), 111, 6843) is converted to the title compound.



## Example 73

Preparation of  
trans-N-(1'-Phenylethyl)-3-carboxy-4-(1H-indol-2"-  
ylcarbonyl)aminoazetidin-2-one



Following the procedure of Example 70, trans-N-(1'-phenylethyl)-3-carboxy-4-dibenzylaminoazetidin-2-one t-butyl ester (T. Hiyama et al., J. Amer. Chem. Soc. (1989), 111, 6843) is converted to the title compound.

## Example 74

Percent displacement of  $^{125}\text{I}$ -CCK-OP binding to rat pancreatic membrane and guinea pig brain homogenates by compounds of the instant invention at different concentrations was used to quantify CCK-A and CCK-B receptor binding, respectively.

Binding of  $^{125}\text{I}$ -CCK-OP to rat pancreas (CCK-A) and guinea pig brain (CCK-B) homogenates.

Rat pancreas or guinea pig brain was homogenized in 50 and 20 volumes, respectively, of 50 mM Tris-HCl buffer (pH 7.8 at 25°C) with a Brinkmann polytron homogenizer. The homogenates were centrifuged twice at 50,000 x g for 20 min with an intermediate rehomogenization in fresh buffer. The final pellets were resuspended in 20 volumes (brain) or 40 volumes (pancreas) of incubation buffer [50 mM Tris-HCl, 5 mM  $\text{MgCl}_2$ , 0.2% BSA, 5 mM dithiothreitol, 0.14 mg/ml bacitracin, pH 7.9 at 25°C]. One milliliter of the final homogenate from brain or pancreas was diluted to 50 mL with incubation buffer to use in the binding assay.

Binding experiments were performed in a final volume of 1 mL in 13x100 mm borosilicate disposable culture tubes. To

duplicate tubes were added 890  $\mu$ L of freshly resuspended pancreas or brain homogenate; 73,000 dpm of  $^{125}$ I-CCK-OP (final concentration, 12 pM) and 10  $\mu$ L of DMSO containing displacing agents (compounds or reference compounds, at the desired final concentrations). Nonspecific (nonsaturable) binding was determined in the presence of 1  $\mu$ M unlabeled CCK-OP. After incubation for 30 min at 37°C the binding was stopped by rapid filtration under a reduced pressure through glass fiber FPD-105 Whatman GF/B filters on Harvester and washed twice with 5 mL of ice-cold Tris buffer (50 mM Tris-HCl, pH 7.8). The radioactivity on the filters was counted in a gamma counter. Radioactivity adsorbed to filters (filter blanks) was less than 0.5% of total radioactivity and was not displaced by the addition of unlabeled CCK-OP. Specific binding was defined as the excess binding over that in blanks containing 1  $\mu$ M unlabeled CCK-OP.

#### Determination of $IC_{50}$ for displacing agents

The ability of compounds to displace  $^{125}$ I-CCK-OP binding to pancreatic or brain membrane homogenate was assessed in duplicate at concentrations varying from  $10^{-5}$  M to  $10^{-7}$  M. When the percent inhibition of specific  $^{125}$ I-CCK-OP binding by

the displacing agent at the highest screening concentration was  $\geq 50\%$ , the compound was considered as active and an  $IC_{50}$  value was determined. The  $IC_{50}$ , the concentration of compound that inhibits 50% of specific  $^{125}I$ -CCK-OP binding, was estimated graphically.

Rat Gastric Emptying Protocol

A test meal for measuring gastric emptying in rats was prepared. Ten grams of methylcellulose (2% solution = 15 centipoises; Aldrich Chemical Company, Milwaukee, WI) was added to 200ml of cold water and mixed at 20,000 rpm in a Waring blender to insure dispersion and hydration of the methylcellulose. In addition, two beef bouillon cubes (Wyler's, Columbus, OH) dissolved in 100ml of warm water was added to the mixture, followed by 16g of casein (Hammersten, Schwartz/Mann, Orangeburg, NY), 8g of powdered confectioners sugar and 8g of cornstarch. The ingredients were mixed for two minutes at 20,000 rpm and the resultant test meal was refrigerated for 48 hours to allow trapped air to escape. Male Charles River Rats, Crl: COBS, CD (SD) BR Strain, 180-200g body weight, were used in groups of six animals. The animals were food deprived for 24 hours prior to the experiment with access to water ad libitum. The compounds to be evaluated were prepared in a 0.5% aqueous methylcellulose solution. If insoluble, the mixture was homogenized for two minutes at 5500 rpm using a Try-R-Stir-R. The compounds were given intraperitoneally or intragastrically at a volume of 5ml/kg, 60 minutes or 90 min, respectively, before the test

meal. Control animals received only the vehicle. Cholecystokinin (100  $\mu$ g/Kg, i.p.) was given 30 minutes before the test meal to delay gastric emptying by an effect elicited through CCK receptors. Sixty minutes after the test meal (2.0ml/rat, i.g.), the rats were sacrificed by CO<sub>2</sub> asphyxiation. The stomachs were removed intact and weighed. The stomachs were kept opened, gently rinsed with tap water, blotted dry with paper toweling, and the empty stomach weighed. The difference between the weight of the full and empty stomach is indicative of the amount of meal remaining in the stomach. The amount of meal remaining in the stomach was subtracted from the weight of 3ml of the test meal to determine the amount of food emptied from the stomach during the test. Weight of the test meal was determined by weighing three samples (3ml) at the beginning and three samples at the end of each experiment and calculating the mean. The mean and standard error of the amount of meal emptied were calculated for at least 5 doses of compound, and expressed as percent change from control. Statistical testing was done for each dose of compound and an ED<sub>50</sub> value was estimated if significant ( $p < 0.05$ ) activity was observed at any dose.

The results of the above protocols for a representative number of compounds of the present invention are shown in Table B.

TABLE B

Example #	COMPOUND	CCK-A BINDING RAT PANCREATIC MEMBRANES: IC50 (uM)	CCK-B BINDING GP BRAIN MEMBRANES: IC50 (uM)	CCK-DELAYED GASTRIC EMPTYING: ED50 or % Reversal @ Dose
41	cis-4-[(2-naphthalenylcarbonyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid	0.015	48% @ 10	ED50 = 0.41 mpk IP
41	trans-4-[(2-naphthalenylcarbonyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid	0.29	22% @ 10	ED50 = 3.2 mpk IP



Example #	COMPOUND	CCK-A BINDING RAT PANCREATIC MEMBRANES: IC50 (uM)	CCK-B BINDING GP BRAIN MEMBRANES: IC50 (uM)	CCK-DELAYED GASTRIC EMPTYING: ED50 or % Reversal @ Dose
44	cis-1-(2-fluorophenyl)- 4-[(2-naphthalenylcarbonyl) amino]-5-oxo-3-pyrrolidinecarboxylic acid	0.062	41% @ 10	86% @ 3 mpk IP ED50 = 1.7 mpk IP
39	trans-4-[(2-naphthalenylcarbonyl) amino-5-oxo-1-pentyl-3-pyrrolidinecarboxylic acid	> 10	--	
28	cis-1-(2-fluorophenyl)- 5-oxo-4-[(3-quinolylcarbonyl) amino]-5-oxo-3-pyrrolidinecarboxylic acid	0.17	> 10	

Example #	COMPOUND	CCK-A BINDING RAT PANCREATIC MEMBRANES: IC50 (uM)	CCK-B BINDING GP BRAIN MEMBRANES: IC50 (uM)	CCK-DELAYED GASTRIC EMPTYING: ED50 or % Reversal @ Dose
27	cis-5-oxo-1-pentyl-4- [(3-quinolinylcarbonyl) amino]-3- pyrrolidinecarboxylic acid, monohydrochloride	0.25	> 10	
29	cis-4-[(1-H-indol-2- ylcarbonyl)amino]-5- oxo-1-phenyl-3- pyrrolidinecarboxylic acid	0.017	5.1	86.3% @ 1.0 mpk IP ED50 < 0.1 mpk IP
30	trans-4-[(1H-indol-2- ylcarbonyl)amino]-5- oxo-1-phenyl-3- pyrrolidinecarboxylic acid	0.32	--	

Example #	COMPOUND	CCK-A BINDING RAT PANCREATIC MEMBRANES: IC50 (uM)	CCK-B BINDING GP BRAIN MEMBRANES: IC50 (uM)	CCK-DELAYED GASTRIC EMPTYING: ED <sub>50</sub> or % Reversal @ Dose
35 (cis)	cis-4-[[ (3,4-dichlorophenyl) carbonyl]amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid	0.058	35% @ 10	57.9% @ 3.0 mpk IP
35 (trans)	trans-4-[[ (3,4-dichlorophenyl) carbonyl]amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid	> 1.0	> 10	

Example #	COMPOUND	CCK-A BINDING RAT PANCREATIC MEMBRANES: IC50 (uM)	CCK-B BINDING GP BRAIN MEMBRANES: IC50 (uM)	CCK-DELAYED GASTRIC EMPTYING: ED <sub>50</sub> or % Reversal @ Dose
32	cis-4-[[[(3,4-dichlorophenyl)carbonyl]amino]-5-oxo-1-pentyl-3-pyrrolidinecarboxylic acid	0.3	49% @ 10	
46 (cis)	cis-4-[[[(4-chlorophenyl)carbonyl]amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid	1.6	> 10	
46 (trans)	cis-4-[[[(4-chlorophenyl)carbonyl]amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid	41	> 10	

Example #	COMPOUND	CCK-A BINDING RAT PANCREATIC MEMBRANES: IC50 (uM)	CCK-B BINDING GP BRAIN MEMBRANES: IC50 (uM)	CCK-DELAYED GASTRIC EMPTYING: ED50 or % Reversal @ Dose
45	trans-4-[[[(4-chlorophenyl)carbonyl]amino]-5-oxo-1-pentyl]-3-pyrrolidinecarboxylic acid	> 1.0	> 10	
40	cis-4-[[[(2-naphthalenylamino)carbonyl]amino]-5-oxo-1-pentyl]-3-pyrrolidinecarboxylic acid	2.8	3.9	
36 (cis)	cis-4-[[[(3,4-dichlorophenyl)amino]carbonyl]amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid	0.10	10.0	

Example #	COMPOUND	CCK-A BINDING RAT PANCREATIC MEMBRANES: IC50 (uM)	CCK-B BINDING GP BRAIN MEMBRANES: IC50 (uM)	CCK-DELAYED GASTRIC EMPTYING: ED50 or % Reversal @ Dose
36 (trans)	trans-4-[[[(3,4-dichlorophenyl)amino]carbonyl]amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid	> 1.0	45% @ 10	
34	cis-4-[[[(3,4-dichlorophenyl)amino]carbonyl]amino]-5-oxo-1-pentyl-3-pyrrolidinecarboxylic acid	0.35	6.0	
47	trans-4-[[[(4-chlorophenyl)amino]carbonyl]amino]-5-oxo-1-pentyl-3-pyrrolidinecarboxylic acid	> 1.0	--	

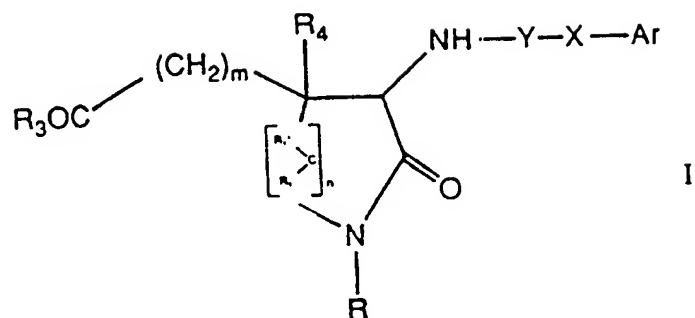
Example #	COMPOUND	CCK-A BINDING RAT PANCREATIC MEMBRANES: IC50 (uM)	CCK-B BINDING GP BRAIN MEMBRANES: IC50 (uM)	CCK-DELAYED GASTRIC EMPTYING: ED50 or % Reversal @ Dose
47	cis-4-[[[(4-chlorophenyl)amino]carbonyl]amino]-5-oxo-1-pentyl-3-pyrrolidinecarboxylic acid	> 1.0		
51	trans-4-[(3-indolyacetyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid	> 1.0	> 10.0	
	1,1-dimethylethyl cis-4-[(2-naphthalenylcarbonyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylate	32% @ 1.0	35% @ 10	

Example #	COMPOUND	CCK-A BINDING RAT PANCREATIC MEMBRANES: IC50 (uM)	CCK-B BINDING GP BRAIN MEMBRANES: IC50 (uM)	CCK-DELAYED GASTRIC EMPTYING: ED50 or % Reversal @ Dose
53	cis-1-[[3-[(2-naphthalenylcarbonyl)amino]-2-oxo-1-phenyl-4-pyrrolidinyl]carbonyl]pyrrolidine	0.75	45% @ 10	
55	trans-1-[[3-[(2-naphthalenylcarbonyl)amino]-2-oxo-1-phenyl-4-pyrrolidinyl]carbonyl]pyrrolidine	27% @ 1.0	10.0	



What we claim is:

1. A compound of the formula



and isomers thereof; or a pharmaceutically acceptable acid or base addition salt thereof:

wherein

Ar is

aryl;

substituted aryl which can be substituted one or more by alkyl of 1 to 6 carbon atoms, alkoxy

wherein the alkyl is 1 to 6 carbon atoms,

trifluoromethyl, halogen, amino, alkyl or dialkyl

substituted amino wherein the alkyl is 1 to 6

carbon atoms; heterounsaturated ring having 5 or 6

carbon atoms wherein one or two of the carbon atoms is replaced by nitrogen, oxygen or sulfur; substituted heterounsaturated ring having 5 or 6 carbon atoms wherein one or two of the carbon atoms is replaced by nitrogen, oxygen or sulfur which can be substituted once or more by alkyl of 1 to 6 carbon atoms, halogen or trifluoromethyl; fused bicyclic aromatic hydrocarbon radical having 9 or 10 carbon atoms; substituted fused bicyclic aromatic hydrocarbon radical having 9 or 10 carbon atoms which can be substituted one or more by alkyl of 1 to 6 carbon atoms, halogen, trifluoromethyl, amino, alkyl or dialkyl substituted amino wherein the alkyl is 1 to 6 carbon atoms or alkoxy wherein the alkyl is 1 to 6 carbon atoms; fused heterobicyclic hydrocarbon radical having 9 or 10 carbon atoms wherein one to three of the carbon atoms is replaced by nitrogen, oxygen or sulfur; substituted fused heterobicyclic hydrocarbon radical having 9 or 10 carbon atoms wherein one to three of the carbon atoms is replaced by nitrogen, oxygen or sulfur which can be substituted one or more by alkyl of 1 to 6 carbon atoms, halogen, trifluoromethyl, amino, alkyl or dialkyl

substituted amino wherein the alkyl is 1 to 6 carbon atoms or alkoxy wherein the alkyl is 1 to 6 carbon atoms;

R is

alkyl having 1 to 8 carbon atoms wherein one of the carbon atoms may be replaced by oxygen;

aryl;

substituted aryl which can be substituted one or more by halogen, alkyl having 1 to 6 carbon atoms, alkoxy wherein the alkyl is 1 to 6 carbon atoms, amino, alkyl or dialkyl substituted amino wherein the alkyl is 1 to 6 carbon atoms, trifluoromethyl, or methylene dioxy; aralkyl wherein the alkyl is 1 to 8 carbon atoms; substituted aralkyl wherein the alkyl is 1 to 8 carbon atoms and the substituent or substituents are selected from the group consisting of halogen, alkyl having 1 to 6 carbon atoms, alkoxy wherein the alkyl is 1 to 6 carbon atoms, amino, alkyl or dialkyl substituted amino wherein the alkyl is 1 to 6 carbon atoms, trifluoromethyl or methylene dioxy;

X is a direct bond or a substituent selected from the group consisting of NH, oxygen or alkylene having 1 to 3 carbon atoms;

n is an integer from 0 to 1;

R<sub>1</sub> and R<sub>1</sub>' are each independently hydrogen or alkyl having 1 to 4 carbon atoms;

m is an integer from 0 to 3;

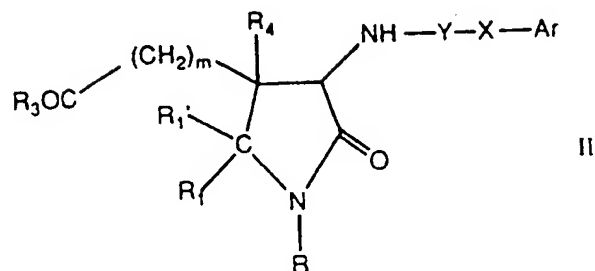
R<sub>3</sub> is OH, OR<sub>5</sub> wherein R<sub>5</sub> is alkyl having 1 to 6 carbon atoms or NR<sub>6</sub>R<sub>7</sub> wherein R<sub>6</sub> and R<sub>7</sub> are each independently hydrogen or alkyl of 1 to 6 carbon atoms or NR<sub>8</sub>R<sub>9</sub> which together form a five to seven membered ring wherein R<sub>8</sub> and R<sub>9</sub> represent an alkylene group having four to six carbon atoms and one of the alkylenes may be optionally replaced by oxygen, nitrogen or NR<sub>10</sub> wherein R<sub>10</sub> represents hydrogen, or alkyl having 1 to 6 carbon atoms or aralkyl wherein the alkyl is 1 to 6 carbon atoms;

R<sub>4</sub> is hydrogen or alkyl having 1 to 4 carbon atoms;

and

Y is C=O or SO<sub>2</sub>.

2. A compound according to Claim 1 having the formula



and isomer thereof; or a pharmaceutically acceptable acid or base addition salt thereof:

wherein

Ar is

aryl;

substituted aryl which can be substituted one or more by alkyl of 1 to 6 carbon atoms, alkoxy

wherein the alkyl is 1 to 6 carbon atoms,

trifluoromethyl, halogen, amino, alkyl or dialkyl

substituted amino wherein the alkyl is 1 to 6

carbon atoms; heterounsaturated ring having 5 or 6

carbon atoms wherein one or two of the carbon atoms

is replaced by nitrogen, oxygen or sulfur;

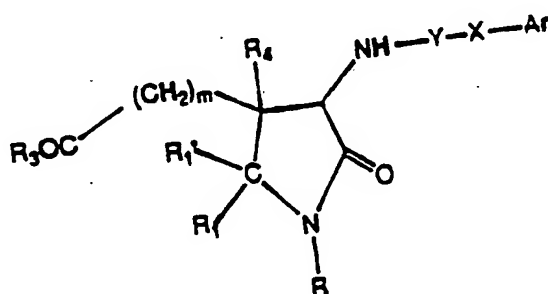
substituted heterounsaturated ring having 5 or 6 carbon atoms wherein one or two of the carbon atoms is replaced by nitrogen, oxygen or sulfur which can be substituted once or more by alkyl of 1 to 6 carbon atoms, halogen or trifluoromethyl; fused bicyclic aromatic hydrocarbon radical having 9 or 10 carbon atoms; substituted fused bicyclic aromatic hydrocarbon radical having 9 or 10 carbon atoms which can be substituted one or more by alkyl of 1 to 6 carbon atoms, halogen, trifluoromethyl, amino, alkyl or dialkyl substituted amino wherein the alkyl is 1 to 6 carbon atoms or alkoxy wherein the alkyl is 1 to 6 carbon atoms; fused heterobicyclic hydrocarbon radical having 9 or 10 carbon atoms wherein one to three of the carbon atoms is replaced by nitrogen, oxygen or sulfur; substituted fused heterobicyclic hydrocarbon radical having 9 or 10 carbon atoms wherein one to three of the carbon atoms is replaced by nitrogen oxygen or sulfur which can be substituted one or more by alkyl of 1 to 6 carbon atoms, halogen trifluoromethyl, amino, alkyl or dialkyl substituted amino wherein the alkyl is 1 to 6

carbon atoms or alkoxy wherein the alkyl is 1 to 6 carbon atoms;

- R is
- alkyl having 1 to 8 carbon atoms wherein one of the carbon atoms may be replaced by oxygen;
- aryl;
- substituted aryl which can be substituted one or more by halogen, alkyl having 1 to 6 carbon atoms, alkoxy wherein the alkyl is 1 to 6 carbon atoms, amino, alkyl or dialkyl substituted amino wherein the alkyl is 1 to 6 carbon atoms, trifluoromethyl or methylene dioxy; aralkyl wherein the alkyl is 1 to 8 carbon atoms; substituted aralkyl wherein the alkyl is 1 to 8 carbon atoms and the substituent or substituents are selected from the group consisting of halogen, alkyl having 1 to 6 carbon atoms, alkoxy wherein the alkyl is 1 to 6 carbon atoms, amino, alkyl or dialkyl substituted amino wherein the alkyl is 1 to 6 carbon atoms, trifluoromethyl or methylene dioxy;
- X is a direct bond or a substituent selected from the group consisting of NH, oxygen or alkylene having 1 to 3 carbon atoms;

- $R_1$  and  $R_1'$  are each independently hydrogen or alkyl having 1 to 4 carbon atoms;
- $m$  is an integer from 0 to 3;
- $R_3$  is OH, OR<sub>5</sub> wherein R<sub>5</sub> is alkyl having 1 to 6 carbon atoms or NR<sub>6</sub>R<sub>7</sub> wherein R<sub>6</sub> and R<sub>7</sub> are each independently hydrogen or alkyl of 1 to 6 carbon atoms or NR<sub>8</sub>R<sub>9</sub> which together form a five to seven membered ring wherein R<sub>8</sub> and R<sub>9</sub> represent an alkylene group having four to six carbon atoms and one of the alkylenes may be optionally replaced by oxygen, nitrogen or NR<sub>10</sub> wherein R<sub>10</sub> represents hydrogen, or alkyl having 1 to 6 carbon atoms or aralkyl wherein the alkyl is 1 to 6 carbon atoms;
- $R_4$  is hydrogen or alkyl having 1 to 4 carbon atoms;
- and
- Y is C=O or SO<sub>2</sub>.

3. A compound according to Claim 2 having the formula





and isomers thereof; or a pharmaceutically acceptable acid or base addition salt thereof:

wherein

Ar is

aryl;

substituted aryl which can be substituted one or more by alkyl of 1 to 6 carbon atoms, alkoxy wherein the alkyl is 1 to 6 carbon atoms, trifluoromethyl, halogen, amino, alkyl or dialkyl substituted amino wherein the alkyl is 1 to 6 carbon atoms; heterounsaturated ring having 5 or 6 carbon atoms wherein one or two of the carbon atoms is replaced by nitrogen, oxygen or sulfur; substituted heterounsaturated ring having 5 or 6 carbon atoms wherein one or two of the carbon atoms is replaced by nitrogen, oxygen or sulfur which can be substituted once or more by alkyl of 1 to 6 carbon atoms, halogen or trifluoromethyl;

R is

alkyl having 1 to 8 carbon atoms wherein one of the carbon atoms may be replaced by oxygen; aryl;

aryl;

substituted aryl which can be substituted one or more by halogen, alkyl having 1 to 6 carbon atoms, alkoxy wherein the alkyl is 1 to 6 carbon atoms, amino, alkyl or dialkyl substituted amino wherein the alkyl is 1 to 6 carbon atoms, trifluoromethyl, or methylene dioxy; or aralkyl wherein the alkyl is 1 to 8 carbon atoms;

$R_1$  and  $R_1'$  are each independently hydrogen or alkyl having 1 to 4 carbon atoms;

$m$  is an integer from 0 to 3;

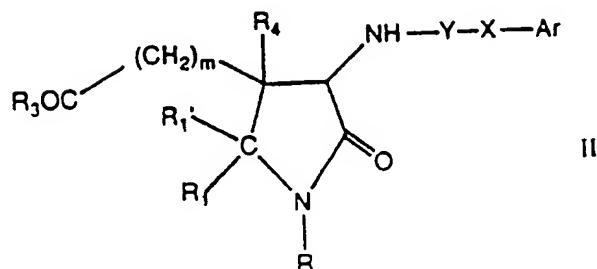
$R_3$  is OH or  $OR_5$  wherein  $R_5$  is alkyl having 1 to 6 carbon atoms;

$R_4$  is hydrogen;

$Y$  is C=O or  $SO_2$ ; and

$X$  is a direct bond or a substituent selected from the group consisting of NH, oxygen, or alkylene having 1 to 3 carbon atoms.

4. A compound according to Claim 1 having the formula



and isomers thereof; or a pharmaceutically acceptable acid or base addition salt thereof:

wherein

Ar is

fused bicyclic aromatic hydrocarbon radical having 9 or 10 carbon atoms; substituted fused bicyclic aromatic hydrocarbon radical having 9 or 10 carbon atoms which can be substituted one or more by alkyl of 1 to 6 carbon atoms, halogen, trifluoromethyl, amino, alkyl or dialkyl substituted amino wherein the alkyl is 1 to 6 carbon atoms, or alkoxy wherein the alkyl is 1 to 6 carbon atoms;

R is

alkyl having 1 to 8 carbon atoms wherein one of the carbon atoms may be replaced by oxygen;

aryl;

substituted aryl which can be substituted one or more by halogen, alkyl having 1 to 6 carbon atoms, alkoxy wherein the alkyl is 1 to 6 carbon atoms, amino, alkyl or dialkyl substituted amino wherein the alkyl is 1 to 6 carbon atoms, trifluoromethyl or methylene dioxy; aralkyl wherein the alkyl is 1 to 8 carbon atoms; substituted aralkyl wherein the alkyl is 1 to 8 carbon atoms and the substituent or substituents are selected from the group consisting of halogen, alkyl having 1 to 6 carbon atoms, alkoxy wherein the alkyl is 1 to 6 carbon atoms, amino, alkyl or dialkyl substituted amino wherein the alkyl is 1 to 6 carbon atoms, trifluoromethyl, or methylene dioxy;

$R_1$  and  $R_1'$  are each independently hydrogen or alkyl having 1 to 4 carbon atoms;

$m$  is an integer from 0 to 3;

$R_3$  is OH,  $OR_5$  wherein  $R_5$  is alkyl having 1 to 6 carbon atoms or  $NR_6R_7$  wherein  $R_6$  and  $R_7$  are each

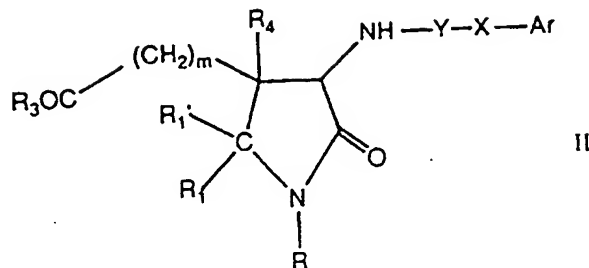
independently hydrogen or alkyl of 1 to 6 carbon atoms or  $\text{NR}_8\text{R}_9$  which together form a five to seven membered ring wherein  $\text{R}_8$  and  $\text{R}_9$  represent an alkylene group having four to six carbon atoms and one of the alkylenes may be optionally replaced by oxygen, nitrogen or  $\text{NR}_{10}$  wherein  $\text{R}_{10}$  represents hydrogen, or alkyl having 1 to 6 carbon atoms or aralkyl wherein the alkyl is 1 to 6 carbon atoms;

$\text{R}_4$  is hydrogen;

$\text{Y}$  is  $\text{C}=\text{O}$  or  $\text{SO}_2$ ; and

$\text{X}$  is a direct bond or a substituent selected from the group consisting of  $\text{NH}$ , oxygen or alkylene having 1 to 3 carbon atoms.

5. A compound according to Claim 1 having the formula



and isomers thereof; or a pharmaceutically acceptable acid or base addition salt thereof:

wherein

Ar is

fused heterobicyclic hydrocarbon radical having 9 or 10 carbon atoms wherein one to three of the carbon atoms is replaced by nitrogen, oxygen or sulfur; substituted fused heterobicyclic hydrocarbon radical having 9 or 10 carbon atoms wherein one to three of the carbon atoms is replaced by nitrogen, oxygen or sulfur which can be substituted one or more by alkyl of 1 to 6 carbon atoms, halogen, trifluoromethyl, amino, alkyl or

dialkyl amino wherein the alkyl is 1 to 6 carbon atoms, or alkoxy wherein the alkyl is 1 to 6 carbon atoms;

R is

alkyl having 1 to 8 carbon atoms;

aryl;

substituted aryl which can be substituted one or more by halogen, alkyl having 1 to 6 carbon atoms, alkoxy wherein the alkyl is 1 to 6 carbon atoms, amino, alkyl or dialkyl substituted amino wherein the alkyl is 1 to 6 carbon atoms, trifluoromethyl or methylene dioxy; aralkyl wherein the alkyl is 1 to 8 carbon atoms; substituted aralkyl wherein the alkyl is 1 to 8 carbon atoms and the substituent or substituents are selected from the group consisting of halogen, alkyl having 1 to 6 carbon atoms, alkoxy wherein the alkyl is 1 to 6 carbon atoms, amino, alkyl or dialkyl substituted amino wherein the alkyl is 1 to 6 carbon atoms, trifluoromethyl or methylene dioxy;

$R_1$  and  $R_1'$  are each independently hydrogen or alkyl having 1 to 4 carbon atoms;

- m is an integer from 0 to 3;
- R<sub>3</sub> is OH, OR<sub>5</sub> wherein R<sub>5</sub> is alkyl having 1 to 6 carbon atoms or NR<sub>6</sub>R<sub>7</sub> wherein R<sub>6</sub> and R<sub>7</sub> are each independently hydrogen or alkyl of 1 to 6 carbon atoms or NR<sub>8</sub>R<sub>9</sub> which together form a five to seven membered ring wherein R<sub>8</sub> and R<sub>9</sub> represent an alkylene group having four to six carbon atoms and one of the alkylenes may be optionally replaced by oxygen, nitrogen or NR<sub>10</sub> wherein R<sub>10</sub> represents hydrogen, or alkyl having 1 to 6 carbon atoms or aralkyl wherein the alkyl is 1 to 6 carbon atoms;
- R<sub>4</sub> is hydrogen;
- Y is C=O; and
- X is a direct bond or a substituent selected from the group consisting of NH, oxygen or alkylene having 1 to 3 carbon atoms.

6. A compound according to Claim 3 which is cis-4-[[[(3,4-dichlorophenyl)carbonyl]amino]-5-oxo-1-pentyl-3-pyrrolidinecarboxylic acid.



8. A compound according to Claim 3 which is trans-4-[[[(4-chlorophenyl)amino]carbonyl]amino]-5-oxo-1-pentyl-3-pyrrolidinecarboxylic acid.
9. A compound according to Claim 3 which is cis-4-[[[(4-chlorophenyl)amino]carbonyl]amino]-5-oxo-1-pentyl-3-pyrrolidinecarboxylic acid.
10. A compound according to Claim 3 which is cis-4-[[[(3,4-dichlorophenyl)amino]carbonyl]amino]-5-oxo-1-pentyl-3-pyrrolidinecarboxylic acid.
11. A compound according to Claim 3 which is cis-4-[[[(4-chlorophenyl)carbonyl]amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid.
12. A compound according to Claim 3 which is trans-4-[[[(4-chlorophenyl)carbonyl]amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid.
13. A compound according to Claim 3 which is cis-4-[[[(3,4-dichlorophenyl)carbonyl]amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid.

14. A compound according to Claim 3 which is trans-4-[[[(3,4-dichlorophenyl)carbonyl]amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid.
15. A compound according to Claim 3 which is trans-4-[[[(3,4-dichlorophenyl)amino]carbonyl]amino-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid.
16. A compound according to Claim 3 which is cis-4-[[[(3,4-dichlorophenyl)amino]carbonyl]amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid.
17. A compound according to Claim 3 which is cis-4-[[[(3,4-dichlorophenyl)sulfonyl]amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid.
18. A compound according to Claim 4 which is trans-4-[(2-naphthalenylcarbonyl)amino-5-oxo-1-pentyl-3-pyrrolidinecarboxylic acid.
19. A compound according to Claim 4 which is cis-1-[(2-fluorophenyl)-4-[(2-naphthalenylcarbonyl)amino]-5-oxo-3-pyrrolidinecarboxylic acid.

20. A compound according to Claim 4 which is cis-4-[(2-naphthalenylamino)carbonyl]amino]-5-oxo-1-pentyl-3-pyrrolidinecarboxylic acid.
21. A compound according to Claim 4 which is cis-4-[(2-naphthalenylcarbonyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid.
22. A compound according to Claim 4 which is trans-4-[(2-naphthalenylcarbonyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid.
23. A compound according to Claim 4 which is cis-1-[[3-[(2-naphthalenylcarbonyl)amino]-2-oxo-1-phenyl-4-pyrrolidinyl]carbonyl]pyrrolidine.
24. A compound according to Claim 4 which is trans-1-[[3-[(2-naphthalenylcarbonyl)amino]-2-oxo-1-phenyl-4-pyrrolidinyl]carbonyl]pyrrolidine.
25. A compound according to Claim 4 which is 1,1-dimethylethyl cis-4-[(2-naphthalenylcarbonyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylate.

26. A compound according to Claim 4 which is cis-4-[(2-naphthalenylsulfonyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid.
27. A compound according to Claim 5 which is cis-4-[(1H-indol-2-ylcarbonyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid.
28. A compound according to Claim 5 which is cis-1-(2-fluorophenyl)-5-oxo-4-[(3-quinolinylcarbonyl)amino]-5-oxo-3-pyrrolidinecarboxylic acid.
29. A compound according to Claim 5 which is trans-4-[(1H-indol-3-ylacetyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid.
30. A compound according to Claim 5 which is cis-5-oxo-1-pentyl-4-[(3-quinolinylcarbonyl)amino]-3-pyrrolidinecarboxylic acid, monohydrochloride.
31. A compound according to Claim 5 which is trans-4-[(1H-indol-2-ylcarbonyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid.

32. A compound according to Claim 5 which is trans-N-[2-oxo-1-phenyl-4-(1-pyrrolidinylcarbonyl)-3-pyrrolidinyl]-1H-indole-2-carboxamide.
33. A compound according to Claim 5 which is cis-4-[(1H-indol-2-ylcarbonyl)amino]-5-oxo-1-(phenylmethyl)-3-pyrrolidinecarboxylic acid.
34. A compound according to Claim 5 which is cis-4-[(1H-indazol-3-ylcarbonyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid.
35. A compound according to Claim 1 which is cis-4-[[3,4-dichlorophenyl)carbonyl]amino]-5-oxo-1-(phenylmethyl)-3-pyrrolidinecarboxylic acid.
36. A compound according to Claim 1 which is cis-4-[(2-naphthalenylcarbonyl)amino]-5-oxo-1-(phenylmethyl)-3-pyrrolidinecarboxylic acid.
37. A compound according to Claim 1 which is cis-5-oxo-1-phenyl-4-[(2-pyrazinylcarbonyl)amino]-3-pyrrolidinecarboxylic acid.

38. A compound according to Claim 1 which is cis-4-[[[(3,4-dichlorophenyl)amino]carbonyl]amino]-5-oxo-1-(methylphenyl)-3-pyrrolidinecarboxylic acid.
39. A pharmaceutical composition useful for treating and preventing cholecystokinin related disorders of the gastrointestinal, central nervous and appetite regulatory systems of mammals comprising at least one compound according to Claim 1, together with one or more non-toxic pharmaceutically acceptable carriers.

40. A pharmaceutical composition according to Claim 39 wherein said compound is selected from the group consisting of

cis-4-[[ (3,4-dichlorophenyl)carbonyl]amino]-5-oxo-1-pentyl-3-pyrrolidinecarboxylic acid

trans-4-[[ (4-chlorophenyl)carbonyl]amino]-5-oxo-1-pentyl-3-pyrrolidinecarboxylic acid

trans-4-[[ [(4-chlorophenyl)amino]carbonyl]amino]-5-oxo-1-pentyl-3-pyrrolidinecarboxylic acid

cis-4-[[ [(4-chlorophenyl)amino]carbonyl]amino]-5-oxo-1-pentyl-3-pyrrolidinecarboxylic acid

cis-4-[[ [(3,4-dichlorophenyl)amino]carbonyl]amino]-5-oxo-1-pentyl-3-pyrrolidinecarboxylic acid

cis-4-[[ (4-chlorophenyl)carbonyl]amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid

trans-4-[[ (4-chlorophenyl)carbonyl]amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid

cis-4-[[ (3,4-dichlorophenyl)carbonyl]amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid

trans-4-[[ (3,4-dichlorophenyl)carbonyl]amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid

trans-4-[[[ (3,4-dichlorophenyl)amino]carbonyl]amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid

trans-4-[(2-naphthalenylcarbonyl)amino]-5-oxo-1-pentyl-3-pyrrolidinecarboxylic acid

cis-1-[(2-fluorophenyl)-4-[(2-naphthalenylcarbonyl)amino]-5-oxo-3-pyrrolidinecarboxylic acid

cis-4-[[ (2-naphthalenylamino)carbonyl]amino]-5-oxo-1-pentyl-3-pyrrolidinecarboxylic acid

cis-4-[(2-naphthalenylcarbonyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid



trans-4-[(2-naphthalenylcarbonyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid

cis-4-[(1H-indol-2-ylcarbonyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid

cis-1-(2-fluorophenyl)-5-oxo-4-[(3-quinolinylcarbonyl)amino]-5-oxo-3-pyrrolidinecarboxylic acid

trans-4-[(1-H-indol-3-ylacetyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid

cis-5-oxo-1-pentyl-4-[(3-quinolinylcarbonyl)amino]-3-pyrrolidinecarboxylic acid, monohydrochloride

trans-4-[(1H-indol-2-ylcarbonyl)-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid

cis-1-[[3-[(2-naphthalenylcarbonyl)amino]-2-oxo-1-phenyl-4-pyrrolidinyl]carbonyl]pyrrolidine

trans-1-[[3-[(2-naphthalenylcarbonyl)amino]-2-oxo-1-phenyl-4-pyrrolidinyl]carbonyl]pyrrolidine

trans-N-[2-oxo-1-phenyl-4-(1-pyrrolidinylcarbonyl)-3-pyrrolidinyl]-1H-indole-2-carboxamide

cis-4-[(1H-indol-2-ylcarbonyl)amino]-5-oxo-1-(phenylmethyl)-3-pyrrolidinecarboxylic acid

1,1-dimethylethyl cis-4-[(2-naphthalenylcarbonyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylate

cis-4-[(2-naphthalenylsulfonyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid

cis-4-[[ (3,4-dichlorophenyl) sulfonyl] amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid

cis-4-[(1H-indazol-3-ylcarbonyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid

cis-5-oxo-1-phenyl-4-[(2-pyrazinylcarbonyl)amino]-3-pyrrolidinecarboxylic acid

cis-4-[(2-naphthalenylcarbonyl)amino]-5-oxo-1-(phenylmethyl)-3-pyrrolidinecarboxylic acid

cis-4-[[ (3,4-dichlorophenyl)carbonyl]amino]-5-oxo-1-(phenylmethyl)-3-pyrrolidinecarboxylic acid

cis-4-[[[(3,4-dichlorophenyl)amino]carbonyl]amino]-5-oxo-1-(methylphenyl)-3-pyrrolidinecarboxylic acid

41. A method for treating and preventing cholecystokinin related disorders of the gastrointestinal, central nervous, and appetite regulatory systems of mammals comprising administering a therapeutically effective dose of at least one compound of Claim 1 to a mammal in need of such treatment.
42. A method according to Claim 41 wherein said compound is selected from the group consisting of

cis-4-[[ (3,4-dichlorophenyl)carbonyl]amino]-5-oxo-1-pentyl-3-pyrrolidinecarboxylic acid

trans-4-[[ (4-chlorophenyl)carbonyl]amino]-5-oxo-1-pentyl-3-pyrrolidinecarboxylic acid

trans-4-[[[(4-chlorophenyl)amino]carbonyl]amino]-5-oxo-1-pentyl-3-pyrrolidinecarboxylic acid

cis-4-[[[(4-chlorophenyl)amino]carbonyl]amino]-5-oxo-1-pentyl-3-pyrrolidinecarboxylic acid

cis-4-[[[(3,4-dichlorophenyl)amino]carbonyl]amino]-5-oxo-1-pentyl-3-pyrrolidinecarboxylic acid

cis-4-[[[(4-chlorophenyl)carbonyl]amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid

trans-4-[[[(4-chlorophenyl)carbonyl]amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid

cis-4-[[[(3,4-dichlorophenyl)carbonyl]amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid

trans-4-[[[(3,4-dichlorophenyl)carbonyl]amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid

trans-4-[[[(3,4-dichlorophenyl)amino]carbonyl]amino-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid

trans-4-[(2-naphthalenylcarbonyl]amino-5-oxo-1-pentyl-3-pyrrolidinecarboxylic acid

cis-1-[(2-fluorophenyl)-4-[(2-naphthalenylcarbonyl)amino]-5-oxo-3-pyrrolidinecarboxylic acid

cis-4-[[ (2-naphthalenylamino)carbonyl]amino]-5-oxo-1-pentyl-3-pyrrolidinecarboxylic acid

cis-4-[(2-naphthalenylcarbonyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid

trans-4-[(2-naphthalenylcarbonyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid

cis-4-[(1-H-indol-2-ylcarbonyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid

cis-1-(2-fluorophenyl)-5-oxo-4-[(3-quinolinylcarbonyl)amino]-5-oxo-3-pyrrolidinecarboxylic acid

trans-4-[(1-H-indol-3-ylacetyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid

cis-5-oxo-1-pentyl-4-[(3-quinolinylcarbonyl)amino]-3-pyrrolidinecarboxylic acid, monohydrochloride

trans-4-[(1H-indol-2-ylcarbonyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid

cis-1-[[3-[(2-naphthalenylcarbonyl)amino]-2-oxo-1-phenyl-4-pyrrolidinyl]carbonyl]pyrrolidine

trans-1-[[3-[(2-naphthalenylcarbonyl)amino]-2-oxo-1-phenyl-4-pyrrolidinyl]carbonyl]pyrrolidine

trans-N-[2-oxo-1-phenyl-4-(1-pyrrolidinylcarbonyl)-3-pyrrolidinyl]-1H-indole-2-carboxamide

cis-4-[(1H-indol-2-ylcarbonyl)amino]-5-oxo-1-(phenylmethyl)-3-pyrrolidinecarboxylic acid

1,1-dimethylethyl cis-4-[(2-naphthalenylcarbonyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylate

cis-4-[(2-naphthalenylsulfonyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid

cis-4-[[3-(3,4-dichlorophenyl)sulfonyl]amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid

cis-4-[(1H-indazol-3-ylcarbonyl)amino]-5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid

cis-5-oxo-1-phenyl-4-[(2-pyrazinylcarbonyl)amino]-3-pyrrolidinecarboxylic acid

cis-4-[(2-naphthalenylcarbonyl)amino]-5-oxo-1-(phenylmethyl)-3-pyrrolidinecarboxylic acid

cis-5-oxo-1-phenyl-4-[(2-pyrazinylcarbonyl)amino]-3-pyrrolidine carboxylic acid

cis-4-[(2-naphthalenylcarbonyl)amino]-5-oxo-1-(phenylmethyl)-3-pyrrolidinecarboxylic acid


cis-4-[[ (3,4-dichlorophenyl)carbonyl]amino]-5-oxo-1-(phenylmethyl)-3-pyrrolidinecarboxylic acid

cis-4-[[ [(3,4-dichlorophenyl)amino]carbonyl]amino]-5-oxo-1-(methylphenyl)-3-pyrrolidinecarboxylic acid

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 91/08648

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (If several classification symbols apply, indicate all) <sup>6</sup>		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int. Cl. 5	C 07 D 207/273	C 07 D 207/277
C 07 D 403/12	A 61 K 31/40	C 07 D 205/085
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched <sup>7</sup>		
Classification System	Classification Symbols	
Int. Cl. 5	C 07 D 207/00 C 07 D 205/00	C 07 D 401/00 C 07 D 403/00
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>8</sup>		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup></b>		
Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
A	US,A,4757068 (W.H. PARSONS) 12-07-1988, see entire document (cited in the application) ---	1-40
A	Journal of Organic Chemistry, vol. 55, no. 3, 1990, D.S. GARVEY et al.: "3,4-disubstituted gamma-lactam rings as conformationally constrained mimics of peptide derivatives containing aspartic acid or norleucine", pages 936-940, see introduction and formula 7 ---	1-40
X	US,A,4260743 (A.K. BOSE) 7 April 1981, see column 15, example 10b; compounds with RN 79007-12-8, 79007-11-7 ---	1
X	DE,A,2748258 (SMITHKLINE) 3 May 1978, see compound with RN 67098-75-3 -----	1
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p><sup>10</sup> Special categories of cited documents :</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p> </div> </div>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
26-02-1992	03.04.93	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE		



## FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☐ OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE <sup>1</sup>

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claim numbers 41, 42 because they relate to subject matter not required to be searched by this Authority, namely:

ALTHOUGH CLAIMS 41, 42 ARE DIRECTED TO A METHOD OF TREATMENT OF (DIAGNOSTIC METHOD PRACTISED ON THE HUMAN/ANIMAL BODY) THE SEARCH HAS BEEN CARRIED OUT AND BASED ON THE ALLEGED EFFECTS OF THE COMPOUND/COMPOSITION.

2. ☐ Claim numbers because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. ☐ Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING <sup>2</sup>

This International Searching Authority found multiple inventions in this International application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the International application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

## Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO.**

US 9108648  
SA 54462

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 24/03/92. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 4757068	12-07-88	None	
US-A- 4260743	07-04-81	None	
DE-A- 2748258	03-05-78	US-A- 4085100	18-04-78
		FR-A,B 2369258	26-05-78
		GB-A- 1592878	08-07-81
		JP-A- 53056696	23-05-78
		NL-A- 7711945	03-05-78

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
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(43) International Publication Date  
10 January 2002 (10.01.2002)

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(10) International Publication Number  
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A61K 31/50 // (C07D 487/04, 241:00), 209:00)

(21) International Application Number: PCT/US01/20962

(22) International Filing Date: 29 June 2001 (29.06.2001)

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60/214,831 29 June 2000 (29.06.2000) US

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SI, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant: **BRISTOL-MYERS SQUIBB PHARMA COMPANY** [US/US]; Patent Dept., P.O. Box 4000, Princeton, NJ 08543-4000 (US).

**Published:**

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(72) Inventors: **PINTO, Donald, J., P.**; 425 Brentford Road, Kennett Square, PA 19348 (US). **QUAN, Mimi, L.**; 113 Venus Drive, Newark, DE 19711 (US).

(88) Date of publication of the international search report:  
25 July 2002

(74) Agent: **BELFIELD, Jing, S.**; Bristol-Myers Squibb Pharma Company, Route 141 & Henry Clay Road, Experimental Station, E353/133B, Wilmington, DE 19898-0353 (US).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/002519 A3

(54) Title: THROMBIN OR FACTOR Xa INHIBITORS

(57) Abstract: This invention relates generally to heteroaryl-phenyl substituted compounds that are inhibitors of trypsin-like serine protease enzymes, especially factor Xa or thrombin, pharmaceutical compositions containing the same, and methods of using the same as anticoagulant agents for treatment and prevention of thromboembolic disorders.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/20962

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D487/04 A61K31/50 A61K31/50 A61K31/50 A61K31/50  
 //(C07D487/04,241:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 28326 A (SIDDIQUI M ARSHAD ;BACHAND BENOIT (CA); IAF BIOCHEM INT (CA); EDMU) 2 July 1998 (1998-07-02) cited in the application claim 28, 2 last cpds; ex. page 40 ---	1-8, 54-57
Y	WO 97 48706 A (SIDDIQUI M ARSHAD ;EDMUNDS JEREMY JOHN (US); WARNER LAMBERT CO (US) 24 December 1997 (1997-12-24) abstract; claims ---	1-8, 54-57
Y	WO 96 19483 A (IAF BIOCHEM INT ;DIMAIO JOHN (CA); SIDDIQUI M ARSHAD (CA); GILLARD) 27 June 1996 (1996-06-27) cited in the application cpds VIII, ex. 495,510,515,640,760,765 --- -/--	1-8, 54-57



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

Date of the actual completion of the international search

4 February 2002

Date of mailing of the international search report

16. 5. 02

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
 Fax: (+31-70) 340-3016

Authorized officer

Frelon, D

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/20962

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	L.S. NARASIMHAN ET AL.: "Structural basis of the thrombin selectivity..." JOURNAL OF MEDICINAL CHEMISTRY, vol. 43, 2000, pages 361-368, XP002188952 WASHINGTON US the whole document	1-8, 54-57
Y	ST-DENIS Y ET AL: "Potent bicyclic lactam inhibitors of thrombin: Part I: P3 modifications" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 8, no. 22, 17 November 1998 (1998-11-17), pages 3193-3198, XP004143725 ISSN: 0960-894X the whole document	1-8, 54-57
Y	PLUMMER J S ET AL: "Potent and selective bicyclic lactam inhibitors of thrombin: part 2: P1 modifications" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 8, no. 23, 1 December 1998 (1998-12-01), pages 3409-3414, XP004143767 ISSN: 0960-894X the whole document	1-8, 54-57
Y	PLUMMER J S ET AL: "Potent and selective bicyclic lactam inhibitors of thrombin: part 3: P1' modifications" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 9, no. 6, 22 March 1999 (1999-03-22), pages 835-840, XP004160484 ISSN: 0960-894X the whole document	1-8, 54-57
A	WO 98 57937 A (DU PONT MERCK PHARMA) 23 December 1998 (1998-12-23) page 191; example 73	1-8, 54-57
A	WO 97 23212 A (DU PONT MERCK PHARMA) 3 July 1997 (1997-07-03) claim 1: cpds IIIa,IIIb	1-8, 54-57

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 01/20962

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 53  
because they relate to subject matter not required to be searched by this Authority, namely:  
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  
1-6,7,8,54,56-57 all in part

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-6(in part),7,8,54(in part),56-57(in part)

Compounds first designated in claim 1, corresponding to compounds claimed in claim 7 and dependent claims thereof

2. Claims: 1-6(in part),9,10,54(in part),56-57(in part)

Compounds further designated in claim 1, corresponding to compounds claimed in claim 9 and dependent claims thereof

3. Claims: 1-6(in part),11,12,54(in part),56-57(in part)

Compounds further designated in claim 1, corresponding to compounds claimed in claim 11 and dependent claims thereof

4. Claims: 1-6(in part),13,14,54(in part),56-57(in part)

Compounds further designated in claim 1, corresponding to compounds claimed in claim 13 and dependent claims thereof

5. Claims: 1-6(in part),15,16,54(in part),56-57(in part)

Compounds further designated in claim 1, corresponding to compounds claimed in claim 15 and dependent claims thereof

6. Claims: 1-6(in part),17,18,54(in part),56-57(in part)

Compounds further designated in claim 1, corresponding to compounds claimed in claim 17 and dependent claims thereof

7. Claims: 1-6(in part),19,20,54(in part),56-57(in part)

Compounds further designated in claim 1, corresponding to compounds claimed in claim 19 and dependent claims thereof

8. Claims: 1-6(in part),21,22,54(in part),56-57(in part)

Compounds further designated in claim 1, corresponding to compounds claimed in claim 21 and dependent claims thereof

9. Claims: 1-6(in part),23,24,54(in part),56-57(in part)

Compounds further designated in claim 1, corresponding to compounds claimed in claim 23 and dependent claims thereof

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

10. Claims: 1-6(in part),25,26,54(in part),56-57(in part)

Compounds further designated in claim 1, corresponding to compounds claimed in claim 25 and dependent claims thereof

11. Claims: 1-6(in part),27,28,54(in part),56-57(in part)

Compounds further designated in claim 1, corresponding to compounds claimed in claim 27 and dependent claims thereof

12. Claims: 1-6(in part),29,30,54(in part),56-57(in part)

Compounds further designated in claim 1, corresponding to compounds claimed in claim 29 and dependent claims thereof

13. Claims: 1-6(in part),31,32,54(in part),56-57(in part)

Compounds further designated in claim 1, corresponding to compounds claimed in claim 31 and dependent claims thereof

14. Claims: 1-6(in part),33,34,54(in part),56-57(in part)

Compounds further designated in claim 1, corresponding to compounds claimed in claim 34 and dependent claims thereof

15. Claims: 1-6(in part),35,36,54(in part),56-57(in part)

Compounds further designated in claim 1, corresponding to compounds claimed in claim 35 and dependent claims thereof

16. Claims: 1-6(in part),37,38,54(in part),56-57(in part)

Compounds further designated in claim 1, corresponding to compounds claimed in claim 37 and dependent claims thereof

17. Claims: 1-6(in part),39,40,54(in part),56-57(in part)

Compounds further designated in claim 1, corresponding to compounds claimed in claim 39 and dependent claims thereof

18. Claims: 1-6(in part),41,42,54(in part),56-57(in part)

Compounds further designated in claim 1, corresponding to compounds claimed in claim 41 and dependent claims thereof



FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

19. Claims: 1-6(in part),43,44,54(in part),56-57(in part)

Compounds further designated in claim 1, corresponding to compounds claimed in claim 43 and dependent claims thereof

20. Claims: 1-6(in part),45,46,54(in part),56-57(in part)

Compounds further designated in claim 1, corresponding to compounds claimed in claim 45 and dependent claims thereof

21. Claims: 1-6(in part),47,48,54(in part),56-57(in part)

Compounds further designated in claim 1, corresponding to compounds claimed in claim 47 and dependent claims thereof

22. Claims: 1-6(in part),49,50,54(in part),56-57(in part)

Compounds further designated in claim 1, corresponding to compounds claimed in claim 49 and dependent claims thereof

23. Claims: 1-6(in part),51,52,54(in part),56-57(in part)

Compounds further designated in claim 1, corresponding to compounds claimed in claim 51 and dependent claims thereof

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim 55 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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Continuation of Box I.1

Claims Nos.: 53

The compounds of claim 53 lack to be properly defined: firstly because they are defined by a result to be achieved (i.e. as trypsin-like serine protease enzyme inhibitors), secondly because the term "P1" is not specified in the claim and has no support in the description (i.e. the expression "inhibitor comprising a P1 group" is not searchable as such).

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/20962

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information on patent family members

International Application No

PCT/US 01/20962

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